

Neurology

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Brain lesions

Frontal lobes lesions

- **Expressive (Broca's) aphasia:**
 - ✓ Located on the posterior aspect of the frontal lobe, in the inferior frontal gyrus.
 - ✓ Speech is non-fluent, laboured, and halting اعرج
- **Disinhibition** السلوك الفاضح
- **Perseveration** الاجتهاد
- **anosmia**
- **inability to generate a list**

Temporal lobe lesion

- **Wernicke's aphasia:**
 - ✓ This area 'forms' the speech before 'sending it' to Brocas area.
 - ✓ Lesions result in word substitution, neologisms الكلمات الجديدة but **speech remains fluent**
- **auditory agnosia**
- **prosopagnosia** (difficulty recognizing faces) , memory problem
- **superior homonymous quadrantanopia**

Parietal lobe lesions

- **sensory inattention**
- **apraxias:** inability to perform particular purposive actions
- **astereognosis** (tactile agnosia)
- **Gerstmann's syndrome** (lesion of dominant parietal): ميعرفش يقرأ...ولا يحسب...ولا يمينه من شماله
- **alexia** or **Dyslexia** (inability to recognise letters or words)
- **Acalculia** (difficulty in calculation)
- **Right/left disorientation**
- **Finger agnosia** (difficulty in identifying the fingers and naming them)
- **inferior homonymous quadrantanopia**
- **Agraphia** (difficulty in writing),

Occipital lobe lesions

- **homonymous hemianopia** (with macula sparing)
- **cortical blindness**
- **visual agnosia**

Cortical blindness:

- The visual cortex is located in the occipital lobes, receiving its blood supply from the posterior cerebral arteries.
- The area for macular vision is in a small area adjacent to the calcarine sulcus.
- **Bilateral occlusion or infarction of the vessels supplying this area results in cortical blindness:**
 - ☒ The visual pathways as far as the cortex are normal and as a result pupillary reactions and fundoscopy are **normal**.
 - ☒ Patients with cortical blindness frequently have **visual hallucinations** and occasionally **deny that they are blind**.

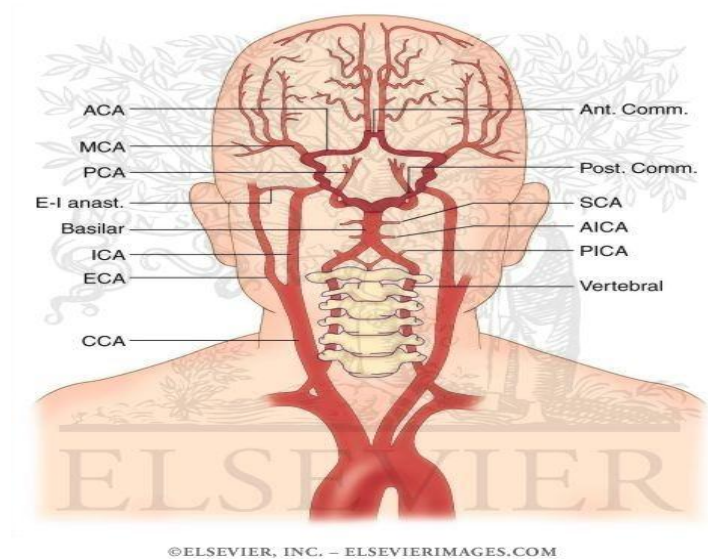
- ☒ **Anton's syndrome:** Visual anosognosia, or the denial of loss of vision, associated with confabulation in the setting of obvious visual loss and cortical blindness
- ☒ **Claude's syndrome** results in ipsilateral third nerve palsy and contralateral cerebellar ataxia and tremor.
- ☒ **Foville's syndrome** causes ipsilateral gaze and facial weakness and contralateral hemiparesis of upper and lower limbs.
- ☒ **Parinaud's syndrome** causes paralysis of upward gaze and accommodation.
- ☒ **Weber's syndrome** results in ipsilateral oculomotor palsy (CN 3 and 4) with contralateral hemiplegia.

Cerebellum lesions

- **Midline Lesions:** gait and truncal ataxia
- **Hemisphere Lesions:** intention tremor, past pointing, dysdiadokinesis, nystagmus

Stroke by anatomy

Site of the lesion	Associated effects
Anterior cerebral artery	➤ Contralateral hemiparesis and sensory loss, ➤ lower extremity > upper
Middle cerebral artery	• Contralateral hemiparesis and sensory loss, • upper extremity > lower • Contralateral homonymous hemianopia • Aphasia (if dominant side usually left)
Posterior cerebral artery	➤ Contralateral homonymous hemianopia with macular sparing ➤ Visual agnosia
Weber's syndrome (branches of the posterior cerebral artery that supply the midbrain)	➤ Ipsilateral CN III palsy ➤ Contralateral weakness (contralateral hemiplegia)
Posterior inferior cerebellar artery (lateral medullary syndrome, Wallenberg syndrome)	➤ Ipsilateral Ataxia, nystagmus ➤ Ipsilateral: facial pain and temperature loss ➤ Contralateral limb/torso pain and temperature loss
Anterior inferior cerebellar artery (lateral pontine syndrome)	➤ Symptoms are similar to Wallenberg's (see above), ➤ but: Ipsilateral: facial paralysis and deafness
Retinal/ophthalmic artery	Amaurosis fugax
Anterior spinal artery occlusion	The lesion is involving the anterior two thirds of the spinal cord which spares light touch, vibration and position sense, but causes loss of pain and temperature distally.



More specific areas

Area	Associated conditions
Medial thalamus and mammillary bodies of the hypothalamus	Wernicke and Korsakoff syndrome
Subthalamic nucleus of the basal ganglia	Hemiballism
Striatum (caudate nucleus) of the basal ganglia	Huntington chorea
Substantia nigra of the basal ganglia	Parkinson's disease
Amygdala	Kluver-Bucy syndrome (hypersexuality, hyperorality, hyperphagia, visual agnosia)

Lacunar strokes

- strong association with HTN
- common sites include BG, thalamus and internal capsule
- present with either
 - ☒ isolated hemiparesis,
 - ☒ hemisensory loss or
 - ☒ hemiparesis with limb ataxia

Pseudoxanthoma elasticum (PXE):

- PXE is a rare heritable connective tissue disorder with autosomal dominant and recessive modes of inheritance.
- It involves the elastic tissues of the eye, skin and cardiovascular system.
- Visual loss can occur by infarction of the visual pathways and optic disc atrophy
- Cerebral ischaemia in PXE is caused by small vessel occlusive disease.

Other neurological complications include:

- 1) Intracranial aneurysms
- 2) Subarachnoid and intracerebral haemorrhages
- 3) Progressive intellectual deterioration
- 4) Mental disturbances, and
- 5) Seizures.

Patients under the age of 60-years-old can be referred for decompressive hemicraniectomy if they have;

- A middle cerebral artery infarct of at least 50% of the MCA territory and have;
 - ⇒ An NIHSS score > 15 and
 - ⇒ A decrease in the level of consciousness to give a score of 1 or more on item 1a of the NIHSS (NICE guidelines).

The only feature that differentiates the middle cerebral artery syndrome from the carotid artery syndrome is amaurosis fugax.

Amaurosis fugax, which is unilateral transient loss of vision that develops over seconds, remains for up to 5 minutes and resolves over 10-20 minutes.

Vertebral artery dissection

- A well-recognized cause of stroke in patients under **45 years** and is associated with a **10% mortality rate** in the acute phase.
- Death may occur due to intracranial dissection, brainstem infarction or subarachnoid hemorrhage.

Common causes include:

- 1) Structural defects of the arterial wall
- 2) Connective tissue disease
- 3) Trauma (for example, road traffic accident, sporting injury), and
- 4) Chiropractic manipulation of the neck. تقويم العمود الفقري

Features

- The typical presentation of vertebral artery dissection is a young person (average age 40 years) with severe occipital headache and neck pain following a recent head or neck injury. The trauma is often trivial, but is usually associated with some form of cervical distortion.
- About 85% of patients develop focal neurological signs due to ischemia of the brain stem or cerebellum.
- The commonest neurological manifestations are symptoms attributable to lateral medullary dysfunction (Wallenberg's syndrome).

Common symptoms and signs include:

- 1) **ipsilateral facial pain and/or numbness** (the most common symptom)
- 2) **vertigo** (very common)
- 3) dysarthria or hoarseness (CN IX and X)
- 4) dysphagia (CN IX and X).
- 5) ipsilateral loss of taste (nucleus and tractus solitarius)
- 6) hiccups
- 7) nausea and vomiting
- 8) diplopia or oscillopsia (image movement experienced with head motion), and

Clinical signs depending upon which areas of the brain stem or cerebellum are affected:

- 1) limb or truncal ataxia
- 2) nystagmus
- 3) ipsilateral Horner syndrome (up to 1/3 patients affected)
- 4) ipsilateral impairment of fine touch and proprioception
- 5) contralateral impairment of pain & thermal sensation in the extremities (spinothalamic tract)
- 6) contralateral hemiparesis
- 7) lateral medullary syndrome
- 8) tongue deviation to the side of the lesion (impairment of CN XII), and
- 9) Internuclear ophthalmoplegia (lesion of the medial longitudinal fasciculus).

Risk factors associated with the development of vertebral artery dissection include:

- judo, yoga
- ceiling painting
- nose blowing
- minor neck trauma
- chiropractor manipulation تقويم العمود الفقري
- hypertension
- oral contraceptive use, and female sex

Other less likely differential diagnoses of stroke in this age group include:

- 1) focal seizure
- 2) migraine with prolonged aura and migraine variants
- 3) multiple sclerosis, and
- 4) Conversion disorders.

Subclavian steal syndrome

- This patient presents with a classic history of subclavian steal syndrome brought on by exercising of his left hand, and associated with a reduction in blood pressure in the left arm.
- Subclavian steal syndrome occurs when there is an occlusion proximal to the origin of the left vertebral artery. As a result blood is stolen from the right vertebral artery with resultant basilar insufficiency.

This is manifest by brainstem features such as:

- Vertigo
- Diplopia
- Dysarthria, and
- Drop attacks.

Risk factors include:

- Hypertension
 - Hypercholesterolaemia
 - Diabetes, and
 - Connective tissue disorders such as Takayasu's arteritis.
-
- Carotid artery dissection can occur spontaneously and is a common cause of young stroke (age less than 40). It typically presents with neck, facial or head pain, ipsilateral Horner's syndrome (miosis and ptosis) and contralateral weakness.

Stroke management

- The Royal College of Physicians (RCP) published guidelines on the diagnosis and management of patients following a stroke in 2004. NICE also issued stroke guidelines in 2008, although they modified their guidance with respect to antiplatelet therapy in 2010.

Selected points relating to the management of acute stroke include:

- ☒ **blood glucose, hydration, oxygen saturation and temperature** should be maintained within normal limits
- ☒ **blood pressure should not be lowered in the acute phase** unless there are complications e.g. Hypertensive encephalopathy
- ☒ **aspirin 300mg** orally or rectally should be given as soon as possible if a hemorrhagic stroke has been excluded
- ☒ with regards to **atrial fibrillation**, the RCP state: 'anticoagulants should not be started until brain imaging has **excluded hemorrhage**, and usually **not until 14 days** have passed from the onset of an ischemic stroke'
- ☒ **If the cholesterol is > 3.5 mmol/l** patients should be commenced on a **statin**. Many physicians will delay treatment until after at least 48 hours due to risk of hemorrhagic transformation

Thrombolysis:

- **Thrombolysis should only be given if:**
 - it is administered within 4.5 hours of onset of stroke symptoms (unless as part of a clinical trial)
 - hemorrhage has been definitively excluded (i.e. Imaging has been performed)
- **Alteplase** is currently recommended by NICE.

Contraindications to thrombolysis:

Absolute	Relative
• Previous intracranial hemorrhage • Intracranial neoplasm • Suspected subarachnoid hemorrhage • Stroke or traumatic brain injury in preceding 3 months • Seizure at onset of stroke • Lumbar puncture in preceding 7 days • Esophageal varices • Active bleeding • Gastrointestinal hemorrhage in preceding 3 weeks • Pregnancy • Acute pancreatitis • Uncontrolled hypertension >200/120mmHg	• Concurrent anticoagulation (INR >1.7) • Hemorrhagic diathesis • Active diabetic hemorrhagic retinopathy • Suspected intracardiac thrombus • Major surgery / trauma in preceding 2 weeks

Secondary prevention:

- NICE also published a technology appraisal in 2010 on the use of clopidogrel and dipyridamole
- **Recommendations from NICE include:**
 - Clopidogrel is now recommended by NICE ahead of combination use of aspirin plus modified release (MR) dipyridamole in people who have had an ischemic stroke
 - Aspirin plus MR dipyridamole is now recommended after an ischemic stroke only if clopidogrel is contraindicated or not tolerated, **but treatment is no longer limited to 2 years' duration**
 - MR dipyridamole alone is recommended after an ischemic stroke only if aspirin or clopidogrel are contraindicated or not tolerated, again with no limit on duration of treatment

With regards to carotid artery endarterectomy:

- recommend if patient has suffered stroke or TIA in the carotid territory and are not severely disabled
- should only be considered if carotid stenosis > 70% according ECST** criteria or > 50% according to NASCET*** criteria

**European Carotid Surgery Trialists' Collaborative Group

***North American Symptomatic Carotid Endarterectomy Trial

Transient ischemic attack

- NICE issued updated guidelines relating to stroke and transient ischemic attack (TIA) in 2008. They advocated use of ABCD2 prognostic score for risk stratifying patient who've had suspected TIA:

A	Age	>60 years	1 point
B	Blood pressure at presentation	>140/90 mmHg	1 point
C	Clinical features	Unilateral weakness	2 points
		Speech disturbance without weakness	1 point
D2	Duration of symptoms	More than 60 minutes	2 points
		10-59 minutes	1 point
	Diabetes	Present	1 point

This gives a total score ranging from 0 to 7:

- People who have had a suspected TIA who are at a higher risk of stroke (ABCD2 score ≥ 4) should have:
 - ☒ aspirin (300 mg daily) started immediately
 - ☒ specialist assessment and investigation within 24 hours of onset of symptoms
 - ☒ measures for secondary prevention introduced as soon as the diagnosis is confirmed, including discussion of individual risk factors
- If the ABCD2 risk score is 3 or below:
 - ☒ specialist assessment within 1 week of symptom onset, including decision on brain imaging
 - ☒ if vascular territory or pathology is uncertain, refer for brain imaging
- People with crescendo TIAs (2 or more episodes in a week)
 - ☒ Should be treated as being at high risk of stroke, even though they may have an ABCD2 score of 3 or below.

Antithrombotic therapy:

(From passmedicine notes)

- clopidogrel is recommended first-line (as for patients who've had a stroke)
- aspirin + dipyridamole should be given to patients who cannot tolerate clopidogrel
- These recommendations follow the 2012 Royal College of Physicians National clinical guideline for stroke.
- These guidelines may change following the CHANCE study (NEJM 2013;369:11). This study looked at giving high-risk TIA patients aspirin + clopidogrel for the first 90 days compared to aspirin alone. 11.7% of aspirin only patients had a stroke over 90 days compared to 8.2% of dual antiplatelet patients
- With regards to carotid artery endarterectomy:
 - recommend if patient has suffered stroke or TIA in the carotid territory and are not severely disabled should only be considered if carotid stenosis > 70% according ECST* criteria or > 50% according to NASCET** criteria

Treatment of TIA:

(From on examination)

- Clopidogrel is the NICE approved treatment of choice for **secondary prevention in stroke**, but is **not licensed for treatment of TIA**.
- NICE TA210² recommends Aspirin and Dipyridamole.
- It is suggested that all patients are started on Aspirin 300mg, and that a choice is made on future antiplatelet therapy at TIA clinic, depending on symptoms, presence of infarction on CT scan, tolerability of drugs, co morbidities.
- Clopidogrel may be preferred in patients who **cannot tolerate dipyridamole**; those with **multivascular disease** (eg coronary or peripheral vascular disease); **those with overt infarction on CT brain**.
- There is no strong evidence regarding appropriate treatment of patient who suffers TIA / stroke whilst on anti-platelet therapy.
- These drugs **reduce**, but do not eliminate, the risk of recurrent stroke/TIA.
- Some patients are resistant to anti-platelet effect of Clopidogrel so can consider changing - also consider cardiac investigations looking for embolic source/arrhythmia.
- There is evidence that **early Aspirin is beneficial for 1-14 days**, but no evidence for immediate initiation of other antiplatelet drugs.

Syringomyelia **(Central cord syndrome)**

- development of cavity (**syrinx**) within the spinal cord
- if extends into medulla then termed **syringobulbia**
- strongly associated with the **Arnold-Chiari malformation**

Features:

- maybe asymmetrical initially
- slowly progressives, possibly over years
- sensory: spinothalamic sensory loss (pain and temperature)
- motor: wasting and weakness of arms
- loss of reflexes, bilateral upgoing plantars
- also seen: Horner's syndrome

Spinal cord compression

- Spinal cord compression is an emergency.
- An urgent MRI spine is essential.
- The whole spine should be imaged because multiple bone metastases are possible.

The commonest tumours to cause spinal cord compression from bone metastases include:

- 1) **lung**
 - 2) **breast**
 - 3) **prostate**
 - 4) **renal and thyroid carcinoma**, and
 - 5) **lymphoma**
-
- ☒ The most appropriate management will be immediate introduction of **high-dose steroids (Dexamethasone 8 mg BD)**: this has been shown to improve overall outcome by reducing mass effect.
 - ☒ An **urgent neurosurgical review** should also be sought.
 - ☒ **Surgery** is the best option for **a single site of metastases** and **radiotherapy** for **multiple sites**. Further imaging by radio-isotope bone scan will be required to determine whether there are any metastases at other bony sites.
 - ☒ **Pamidronate** is only used to correct hypercalcaemia from malignancies and bone pain secondary to osteoporosis.
 - ☒ **Chemotherapy** would be indicated in chemosensitive tumours such as lymphoma.
 - ☒ **In summary**, the treatment for spinal cord compression includes high doses of steroids following by either surgery (single site) or radiotherapy (multiple sites) or chemotherapy (lymphoma).

Subarachnoid hemorrhage

- Classically presents with a thunderclap headache يشبه الرعد and neck stiffness
- Usually occurs spontaneously

Causes:

- 1) 85% are due to rupture of berry aneurysms (conditions associated with berry aneurysms include APCKD, Ehlers-Danlos syndrome and coarctation of the aorta)
- 2) AV malformations
- 3) trauma
- 4) tumours

Investigations:

- ☒ **CT:** negative in 5%
- ☒ **LP:**
 - ✓ **done after 12 hrs** (allowing time for xanthochromia to develop)
 - ✓ If the CSF examination revealed **xanthochromia**, or there was still a high level of clinical suspicion, then **cerebral angiography** would be the next step.
- ☒ **Cerebral angiography:**
 - ✓ If the CSF examination revealed xanthochromia, or
 - ✓ there was still a high level of clinical suspicion

Complications:

- 1) **Rebleeding** (in 30%)
- 2) **obstructive hydrocephalus** (due to blood in ventricles)
- 3) **vasospasm** leading to cerebral ischemia

Management:

- 1) **neurosurgical opinion:**
 - ☒ no clear evidence over early surgical intervention against delayed intervention
- 2) **Nimodipine:**
 - ☒ **60mg / 4 hrly** (if BP allows)
 - ☒ has been shown to reduce the severity of neurological deficits but doesn't reduce rebleeding*

The way nimodipine works in subarachnoid hemorrhage is not fully understood. It has been previously postulated that it reduces cerebral vasospasm (hence maintaining cerebral perfusion) but this has not been demonstrated in studies

The most common cause of an isolated deep intracerebral hemorrhage in the basal ganglia is hypertension.

The Hunt and Hess scale grades subarachnoid hemorrhage (SAH) thus:

- 1) Asymptomatic or minimal headache & slight neck stiffness
- 2) Moderate or severe headache with neck stiffness, but no neurological deficit other than cranial nerve palsy
- 3) Drowsiness with confusion or mild focal neurology
- 4) Stupor with moderate to severe hemiparesis or mild decerebrate rigidity
- 5) Deeply comatose with severe decerebrate rigidity.

Severity and mortality increase with grade.

Cerebral ischemia

- May be delayed as a result of **delayed cerebral ischemia** (DCI) or **cerebral vasospasm**
- It is the most common cause of death and disability following aneurysmal subarachnoid hemorrhage (SAH).
- It may lead to death or permanent neurologic deficits in over 17-40% patients following SAH.
- The clinical diagnosis of DCI is made when the patient experiences an altered level of consciousness or a new focal neurologic deficit following an initial bleed.
- Typically the development of DCI starts **on day 3 after** the initial SAH and is maximal at **day 5-14** and **resolves on day 21**.
- The calcium channel antagonist **nimodipine** has been shown to improve neurological outcome and the reduction of the incidence of cerebral vasospasm.
- There is no statistical evidence from controlled studies for a beneficial effect of triple-H therapy (hypertension, hypervolaemia and haemodilution) or the individual components on cerebral blood flow (CBF) following SAH.
- In some studies hypertension is more effective in increasing CBF than hypervolaemia or haemodilution.
- Secondary effects of SAH include increased intracranial pressure, destruction of brain tissue by intracerebral hemorrhage, tentorial shift and brain herniation, all of which contribute to pathology.
- Patients often survive these complications, but may deteriorate more than 24 hours later from DCI. This can cause serious morbidity or death in up to 30% of patients with SAH.
- DCI may result from angiographic vasospasm, cortical spreading ischemia, arteriolar constriction and thrombosis.

Treatment for DCI includes prophylactic administration of **nimodipine**, and **current neurointensive care**.

Subdural hemorrhage

- most commonly secondary to trauma e.g. **old person/alcohol falling over**
- Risk factors include old age, alcoholism and anticoagulation
- initial injury may be minor and is often forgotten
- caused by bleeding from damaged **bridging veins** between cortex and venous sinuses
- Most commonly occur around the **frontal** and **parietal** lobes

Features:

- **headache**
- **classically fluctuating conscious level**
- **raised ICP**

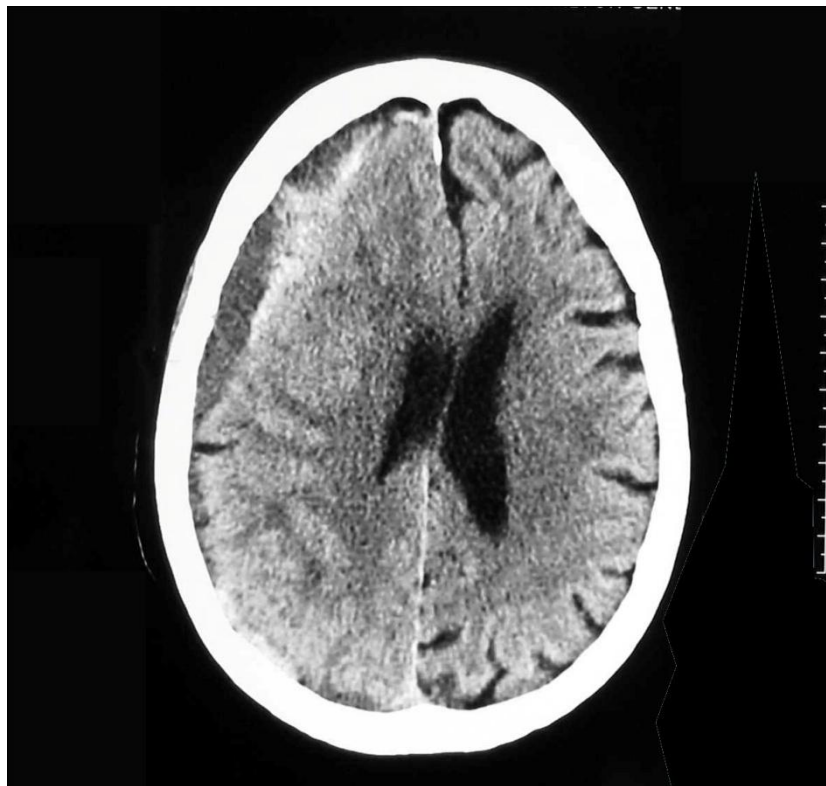
Treatment:

- Needs neurosurgical review? burr hole

Fluctuating consciousness = subdural hemorrhage

- The combination of falls, alcohol excess, fluctuating episodes of confusion and focal neurology points towards a diagnosis of subdural hemorrhage.
- The phrase 'fluctuating conscious level' is common in questions and should always bring to mind subdural hemorrhage

S---S→ Slower onset of symptoms than extradural



Chronic subdural hemorrhage

Head injury

- NICE has strict and clear guidance regarding which adult patients are safe to discharge and which need further CT head imaging.

Who require an immediate CT head and who require CT head within 8 hours of injury:

CT head immediately:

- GCS < 13 on initial assessment
- GCS < 15 at 2 hours post-injury
- Suspected open or depressed skull fracture.
- Any sign of basal skull fracture (haemotympanum, 'panda' eyes, Battle's sign, CSF fluid leakage from the ear or nose).
- Post-traumatic seizure.
- Focal neurological deficit.
- more than 1 episode of vomiting

CT head scan within 8 hours of the head injury - for adults with any of the following risk factors who have experienced some loss of consciousness or amnesia since the injury:

- age 65 years or older
- any history of bleeding or clotting disorders
- If a patient is on warfarin who has sustained a head injury with no other indications for a CT head scan, perform a CT head scan within 8 hours of the injury.
- dangerous mechanism of injury:
 - ☒ a pedestrian مشاة or cyclist struck by a motor vehicle,
 - ☒ an occupant ejected from a motor vehicle or
 - ☒ a fall from a height of greater than 1 metre or 5 stairs
- > 30 minutes' retrograde amnesia of events immediately before the head injury

Battle's sign:

- Mastoid ecchymosis, is an indication of fracture of middle cranial fossa, and may suggest underlying brain trauma.
- Battle's sign consists of bruising over the mastoid process, as a result of extravasation of blood along the path of the posterior auricular artery.
- this sign will take at least one day to appear after the initial traumatic Basilar skull fracture, similar to Raccoon eyes.
- Battle's sign may be confused with a spreading hematoma from a fracture of the mandibular condyle, which is a less serious injury.

Types of traumatic brain injury

Primary brain injury may be **focal** (contusion/haematoma) or **diffuse** (diffuse axonal injury)

1) Diffuse axonal injury (DAI)

- Extensive lesions in white matter tracts over a widespread area.
- DAI is one of the most common types of traumatic brain injury and is a major cause of unconsciousness and persistent vegetative state after head trauma
- It occurs in about half of all cases of severe head trauma.
- The outcome is frequently coma, with over 90% of patients with severe DAI never regaining consciousness.
- Those who wake up often remain significantly impaired.
- DAI can occur from very mild or moderate to very severe.
- Concussion may be a milder type of diffuse axonal injury

2) Intra-cranial haematomas can be extradural, subdural or intracerebral,

3) contusions may occur adjacent to (coup) or contralateral (contre-coup) to the side of impact

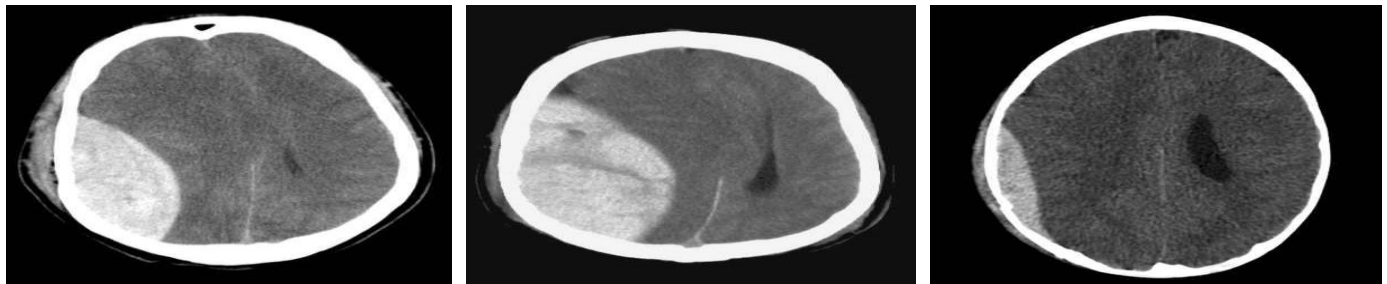
4) Secondary brain injury occurs when cerebral oedema, ischemia, infection, tonsillar or tentorial herniation exacerbates the original injury.

5) The normal cerebral auto regulatory processes are **disrupted** following trauma rendering the brain more susceptible to blood flow changes and hypoxia

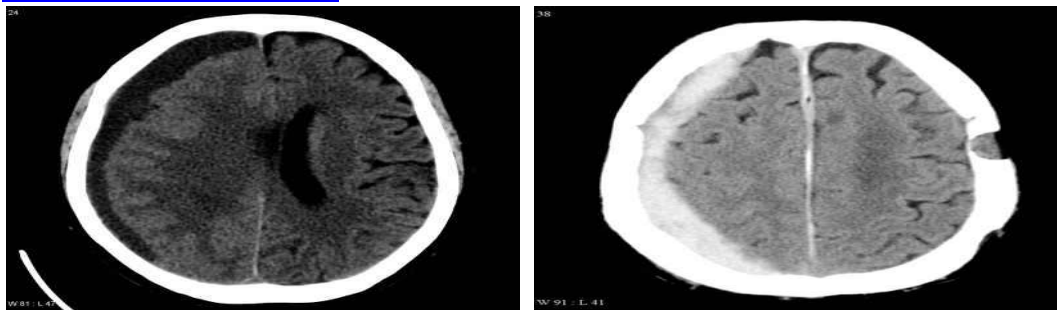
6) The Cushings reflex (**HTN** & **bradycardia**) often occurs late and is usually a preterminal event

Type of injury	Notes
Extradural (epidural) haematoma ExTra → Temporal	- Bleeding into the space between the dura mater and the skull (narrow space & arterial bleeding → history would be acute as the haematoma expands quickly within the limited extradural space). - Often results from acceleration-deceleration trauma or a blow to the side of the head. - The majority of epidural haematomas occur in the temporal region where skull fractures cause a rupture of the middle meningeal artery. Features: ➤ features of raised intracranial pressure ➤ some patients may exhibit a lucid interval
Subdural haematoma	- Bleeding into the outermost meningeal layer. - Most commonly occur around the frontal and parietal lobes. - Risk factors include old age, alcoholism and anticoagulation. - Slower onset of symptoms than an epidural haematoma.
Subarachnoid hemorrhage	Usually occurs spontaneously in the context of a ruptured cerebral aneurysm but may be seen in association with other injuries when a patient has sustained a traumatic brain injury

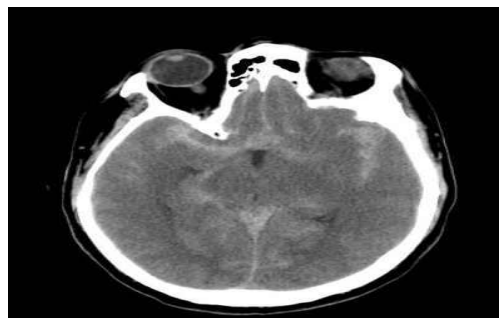
Extradural (epidural) haematoma:



Subdural haematoma:



Subarachnoid hemorrhage:



- This is a non-contrast CT head which demonstrates a well circumscribed high attenuation lesion with some surrounding oedema in the frontal lobe (A) consistent with an intracranial haematoma.



- Acute cerebral infarcts are typically hypodense with vasogenic oedema, they conform to arterial blood supply territories and are typically wedge-shaped (when not lacunar).
- Cerebral abscesses are usually hypodense with surrounding oedema, peripheral ring enhancement is characteristically seen when contrast is administered.
- Acute extradural and subdural haematomas would both be high attenuation however both are anatomically located next to the skull - extradural haematomas have a convex border whilst subdural haematomas have a concave border. Acutely blood is high attenuation (bright) on CT, as time passes the degree of attenuation decreases and the area eventually becomes hypodense. Care must be taken not to miss bleeds when they are isodense with cerebral tissue.

Intracranial venous thrombosis

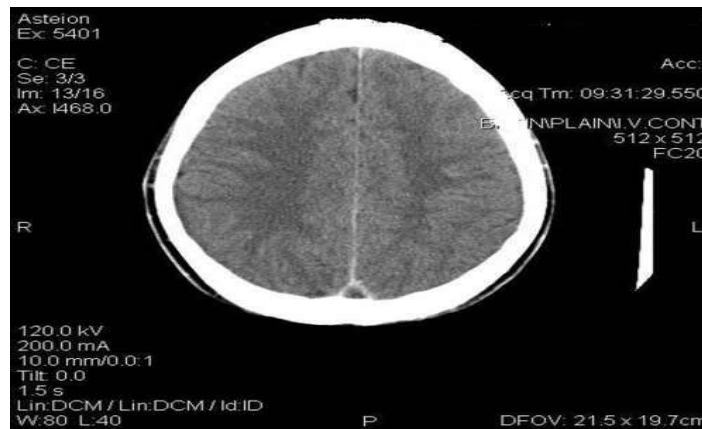
- can cause cerebral infarction, much less common than arterial causes
- 50% of patients have **isolated sagittal sinus thrombosis**
- the remainder have coexistent lateral sinus thromboses and cavernous sinus thromboses

Features:

- headache (may be sudden onset)
- nausea & vomiting

Sagittal sinus thrombosis

- may present with seizures and hemiplegia
- parasagittal--- biparietal or bifrontal hemorrhagic infarctions are sometimes seen



CT with contrast demonstrating a superior sagittal sinus thrombosis showing the typical empty delta sign. Look at the 'bottom' of the scan for the triangular shaped dural sinus. This should normally be white due to it being filled with contrast. The empty delta sign occurs when the thrombus fails to enhance within the dural sinus and is outlined by enhanced collateral channels in the falx. This sign is seen in only about 25%-30% of cases but is highly diagnostic for sagittal sinus thrombosis

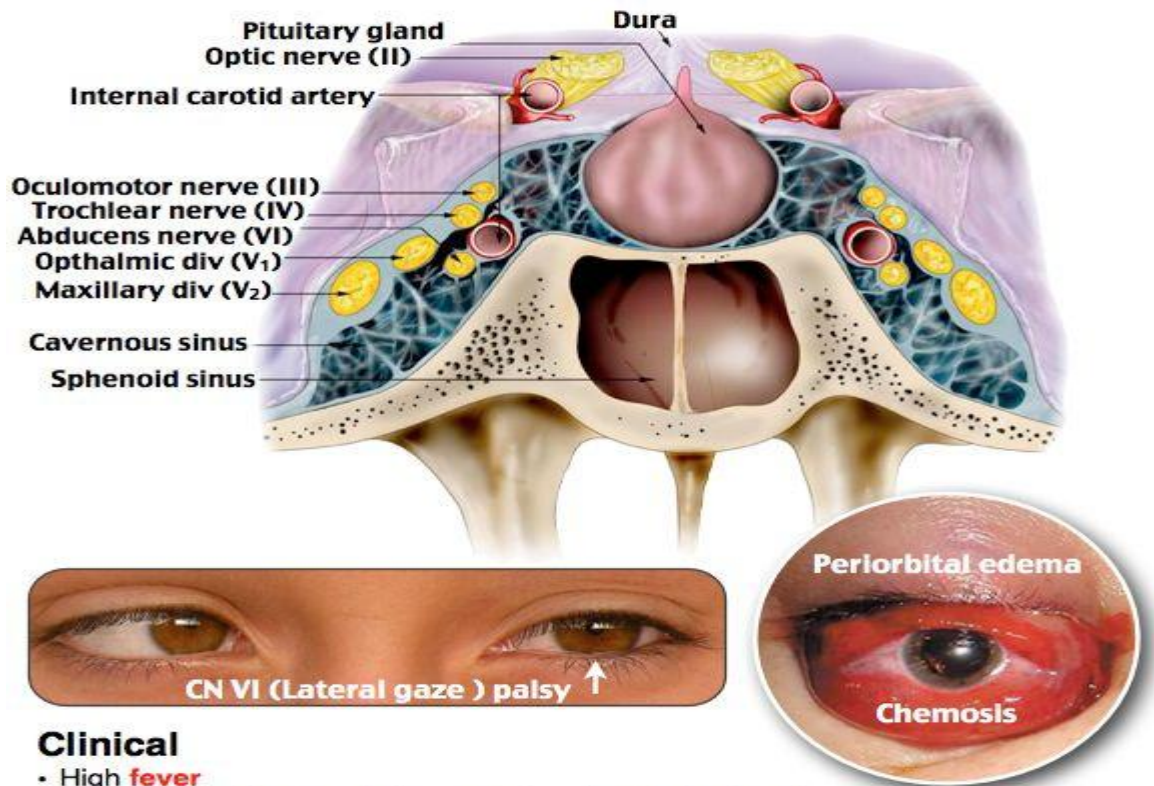
Cavernous sinus thrombosis

- Periorbital oedema
- ophthalmoplegia: 6th nerve damage typically occurs before 3rd & 4th
- trigeminal nerve involvement may lead to hyperaesthesia of upper face and eye pain
- central retinal vein thrombosis

Causes of cavernous sinus syndrome:

- 1) local infection (e.g. sinusitis),
- 2) neoplasia,
- 3) trauma

Cavernous Sinus Thrombosis



Clinical

- High **fever**
- **Periorbital edema** and **chemosis** (conjunctival edema)
- **Cranial nerve palsies** (CN VI most common)
- Decreased **visual acuity**

Dx

- CT scan
- MRI

Rx

- IV ABX
- Heparin
- **Surgical** consultation

Lateral sinus thrombosis

- 6th and 7th cranial nerve palsies

Epilepsy

- two main categories: generalized and partial seizures
- partial seizures may progress to general seizures
- other types: myoclonic, atypical absence, atonic and tonic seizures are usually seen in childhood

Generalized - no focal features, consciousness lost immediately

- grand mal (tonic-clonic)
- petit mal (absence seizures)
- myoclonic: brief, rapid muscle jerks
- partial seizures progressing to generalised seizures

Partial - focal features depending on location

- simple (no disturbance of consciousness or awareness)
- complex (consciousness is disturbed)
- temporal lobe → aura, déjà vu, jamais vu;
- motor → Jacksonian

A Jacksonian seizure:

- Also known as a focal (partial) motor seizure.
- In this condition an uncontrolled, spontaneous discharge of electricity from one motor cortex presents with contralateral motor signs.
- The patient has preserved consciousness as it is a partial seizure and after the seizure it is common to have a Todd's paralysis where the limb is weak.

Temporal lobe epilepsy:

- Presents with the sensation of déjà vu or an unreal feeling and can progress to hallucinations and altered conscious level.

Generalized epilepsy

Absence seizures (petit mal)

- Absence seizures are a form of generalized epilepsy that is mostly seen in children.
- The typical age of onset of 3-10 years old and girls are affected twice as commonly as boys

Features:

- absences last a few seconds and are associated with a quick recovery
- seizures may be provoked by hyperventilation or stress
- the child is usually unaware of the seizure
- they may occur many times a day
- EEG: bilateral, symmetrical 3Hz spike and wave pattern

Management:

- ☒ sodium valproate and ethosuximide are first-line treatment
- ☒ good prognosis: 90-95% become seizure free in adolescence
- ☒ carbamazepine may actually exacerbate absence seizure

Juvenile Myoclonic Epilepsy

- The commonest of the idiopathic generalised epilepsies.
 - Seizures types include
 - ☒ Absences
 - ☒ Myoclonic jerks and
 - ☒ Tonic-clonic seizures which tend to occur within an hour of waking.
 - Precipitating factors include alcohol, menstruation and sleep deprivation.
 - The condition is genetically linked to the short arm of chromosome 6.
 - Prognosis is extremely favourable if the condition is treated correctly, with many patients becoming seizure-free. No developmental delay and has no abnormalities on imaging or blood tests.
 - Treatment options include sodium valproate, lamotrigine and topiramate.
 - Lifelong drug treatment is usually necessary to avoid relapses in patients who achieve seizure-free status on medication.
-
- vasovagal syncope has characteristic warning symptoms of feeling hot and blurring of vision with quick recovery.
 - Patients with syncope can commonly have jerking of the limbs when they are unconscious and this does not mean they have had a seizure.
 - Tilt table testing is useful to support the diagnosis of vasovagal syncope.

Epilepsy treatment

- Most neurologists now start antiepileptics following a **second epileptic seizure**.
- NICE guidelines suggest **starting antiepileptics after the first seizure if any of the following are present:**
 - the patient has a neurological deficit
 - brain imaging shows a structural abnormality
 - the EEG shows unequivocal epileptic activity
 - the patient or their family or carers consider the risk of having a further seizure unacceptable
- **Sodium valproate** is considered the first line treatment for patients with **generalised seizures**.
- **Carbamazepine** (Tegretol) used for **partial seizures**

Generalised tonic-clonic seizures

- ☒ First line: **sodium valproate**(Depacon)
- ☒ second line: lamotrigine, carbamazepine (Tegretol)

Absence seizures (Petit mal)

- ☒ First line : **sodium valproate** or **ethosuximide**
- ☒ sodium valproate particularly effective if co-existent tonic-clonic seizures in primary generalised epilepsy
- ☒ carbamazepine may actually **exacerbate** absence seizure

Myoclonic seizures:

- ☒ **sodium valproate**
- ☒ second line: clonazepam, lamotrigine

Partial seizures:

- ☒ **First line : carbamazepine**
- ☒ second line: **lamotrigine****, sodium valproate

**the 2007 SANAD study indicated that lamotrigine may be a more suitable first-line drug for partial seizures although this has yet to work its way through to guidelines

- + Stopping of Antiepileptic Drugs (AED) can be considered if seizure free for > 2 years
- + But should be stopped over 2-3 months
- + Benzodiazepines should be stopped over a longer period

Management of status epilepticus

- 1) **Protect airway.**
- 2) **Give oxygen 10 L/min** via high-flow mask.
- 3) Administer **benzodiazepine** IV or rectally. **Lorazepam** is preferred because of long duration of anti-epileptic effect. This is effective in ~80% cases.
- 4) **If the patient does not respond**, the regime may be **repeated after 5-10 minutes** using the same or a different benzodiazepine.
- 5) **If seizures recur or fail to respond after 30 minutes a parenteral anti-epileptic agent should be started.**
 - ☒ **Intravenous phenytoin** is usually used and is given as a loading dose of 18 mg/kg.
 - ☒ Adverse effects are common and include **CNS depression** and **cardiac arrhythmias**.
 - ☒ If the patient is already taking phenytoin, either IV phenytoin or fosphenytoin should still be given: it is likely that plasma levels are subtherapeutic.
- 6) The anaesthetic agents **thiopental** and **propofol** may be effective in controlling status epilepticus if the above measures fail (unlicensed indication) but should only be done with full intensive care support.

Fosphenytoin, a disodium phosphate ester of phenytoin,

Has several advantages over phenytoin:

- it can be given IV or IM (phenytoin can only be given IV) and can be given at infusion rates three times faster than phenytoin
- therapeutic levels are achieved within 10 minutes, and
- it has a lower incidence of adverse events than phenytoin

Fosphenytoin is **a pro-drug** of phenytoin - metabolised in the body to phenytoin and endogenous phosphates.

Antiepileptic drugs side effects

Sodium valproate is associated with:

- 1) nausea
- 2) increased appetite and weight gain
- 3) alopecia: regrowth may be curly
- 4) ataxia
- 5) tremor
- 6) hepatitis
- 7) pancreatitis
- 8) thrombocytopaenia
- 9) teratogenic
- 10) hyponatraemia
- 11) Polycystic ovary disease PCO

Lamotrigine is associated with:

- Skin rash
- Stevens-Johnson syndrome in severe cases.



Phenytoin is associated with: (SEGAD) see pharma

- Peripheral neuropathy
- Cerebellum like syndrome:
 - ☒ Atrophy of the cerebellum.
 - ☒ The degree of atrophy is related to the duration of phenytoin and is not to dosage.
- Acne
- Hirsutism
- Stevens-Johnson syndrome
- Gingival hypertrophy
- Vitamin D deficiency → Hypocalcaemia.
- Drug induced Lupus.
- Teratogenic.
- aplastic anemia
- Megaloplastic aneamia

Vigabatrin: V----Visual

- Antiepileptic
- 40% of patients develop visual field defects, which may be irreversible
- visual fields should be checked every 6 months

Epilepsy in pregnancy and breast feeding

- The risks of uncontrolled epilepsy during pregnancy generally outweigh the risks of medication to the fetus.
- All women thinking about becoming pregnant should be advised to take **folic acid 5mg** per day well before pregnancy to minimise the risk of **neural tube defects**.
- Around 1-2% of newborns born to non-epileptic mothers have congenital defects.
- This rises to 3-4% if the mother takes antiepileptic medication.

Other points

- aim for **monotherapy**
- there is no indication to monitor antiepileptic drug levels
- **Carbamazepine**: often considered **the least teratogenic** of the older antiepileptics
- **sodium valproate**: associated with **neural tube defects**
- **phenytoin**:
 - ✓ associated with **cleft palate**
 - ✓ **clotting disorders**: It is advised that pregnant women taking phenytoin are given **vitamin K** in the last month of pregnancy to prevent **clotting disorders** in the newborn
- **Lamotrigine**:
 - ✓ Studies to date suggest **the rate of congenital malformations may be low**.
 - ✓ The dose of lamotrigine may need to be increased in pregnancy
- **Breast feeding is generally considered safe** for mothers taking antiepileptics with the possible exception of the **barbiturates**

Sodium valproate مهمة

- The November 2013 issue of the Drug Safety Update also carried a warning about new evidence showing a significant risk of **neuro-developmental delay** in children following maternal use of sodium valproate.
- The update concludes that sodium valproate **should not be used** during pregnancy and in women of childbearing age unless clearly necessary.
- Women of childbearing age should not start treatment without specialist neurological or psychiatric advice.

Pseudoseizures

Factors favouring pseudoseizures

- pelvic thrusting
- family member with epilepsy
- more common in females
- crying after seizure
- don't occur when alone
- gradual onset

Factors favouring true epileptic seizures

- tongue biting
- raised serum prolactin* (not fully understood)

☒ **Video telemetry** is useful for differentiating

* It is hypothesised that there is spread of electrical activity to the ventromedial hypothalamus, leading to release of a specific prolactin regulator into the hypophyseal portal system

Multiple sclerosis

- **Chronic cell-mediated** autoimmune disorder
- Characterised by **demyelination** in the CNS.
- 3 times more common in women
- most commonly diagnosed in people aged 20-40 years
- much more common at higher latitudes (5 times more common than in tropics)

Genetics:

- monozygotic twin concordance = 30%
- dizygotic twin concordance = 2%

Subtypes:

Relapsing-remitting disease

- most common form, accounts for around **80%** of patients
- acute attacks (e.g. last 1-2 months) followed by periods of remission

Secondary progressive disease

- describes relapsing-remitting patients who have deteriorated and have developed neurological signs and symptoms between relapses
- around 65% of patients with relapsing-remitting disease go on to develop secondary progressive disease within **15 years** of diagnosis
- **gait** and **bladder** disorders are generally seen

Primary progressive disease

- accounts for **10%** of patients
- progressive deterioration from onset
- more common in **older people**

Features of Multiple sclerosis:

Patients may present with non-specific features; around 75% of patients have **significant lethargy**

Visual:

- **optic neuritis**: common presenting feature
- **optic atrophy**
- **Uhthoff's phenomenon**: worsening of vision following **rise in body temperature**
- **internuclear ophthalmoplegia** The commonest cause of unilateral INO in young person in UK

Sensory:

- pins/needles and **numbness**, Sensory symptoms lasting for weeks are common in MS
- trigeminal neuralgia
- **Lhermitte's syndrome**: **paraesthesiae** in limbs on neck flexion

Motor: spastic weakness: most commonly seen in the **legs**

Cerebellar:

- ataxia: more often seen during an acute relapse than as a presenting symptom
- tremor

Others:

- urinary incontinence
- sexual dysfunction
- intellectual deterioration

Multiple sclerosis investigation:

Diagnosis requires demonstration of lesions **disseminated** in time and space

MRI:

- **high signal** T2 lesions
- **periventricular** plaques

CSF:

- **oligoclonal bands** (and not in serum) مهمة في الاسئلة
- increased intrathecal synthesis of IgG

Visual evoked potentials: VEP

- **delayed**, but well preserved waveform

Multiple sclerosis management:

- Treatment in multiple sclerosis is focused at reducing the frequency and duration of relapses.
- There is no cure.

Acute relapse:

High dose steroids:

- ☒ **IV methylprednisolone** may be given for **3-5 days** to shorten the length of an acute relapse.
- ☒ It should be noted that steroids shorten the duration of a relapse and do not alter the degree of recovery (i.e. whether a patient returns to baseline function)

Disease modifying drugs

Beta-interferon:

- ☒ Has been shown to reduce the relapse rate by up to 30% for the first two years of treatment.
- ☒ reduces number of relapses and MRI changes, however doesn't reduce overall disability
- ☒ Certain criteria have to be met before it is used:
 - ✓ relapsing-remitting disease + 2 relapses in past 2 years + able to walk 100m unaided
 - ✓ secondary progressive disease + 2 relapses in past 2 years + able to walk 10m (aided or unaided)

The Association of British Neurologists criteria (ABN) for commencing beta-interferon:

- 1) Has had more than two separate episodes within the last two years
- 2) Is more than 18-years-old, and
- 3) Can walk more than 100 metres.

Contraindications to beta-interferon are:

- 1) History of severe clinical **depression**
- 2) Uncontrolled **epilepsy**
- 3) Hepatic dysfunction, and
- 4) Myelosuppression.

There are three products used;

- ☒ **Beta-interferon 1a (Avonex and Rebif)**,
⇒ both of which are licensed for relapsing-remitting MS and
- ☒ **Beta-interferon 1b (Betaferon)**,
⇒ licensed for both relapsing remitting and secondary progressive forms of MS
- ☒ **3 or more relapses** per year ⇒ **stop the interferons** or **glatiramer acetate** injections (as the objective behind using them is to reduce relapse frequency).

Other drugs used in the management of multiple sclerosis:

- 1) **Glatiramer acetate:** immunomodulating drug - acts as an 'immune decoy'
 - 2) **Natalizumab:**
 - ✓ A recombinant **monoclonal antibody** that
 - ✓ **Antagonises Alpha-4 Beta-1-integrin** found on the surface of leucocytes,
 - ✓ thus inhibiting migration of leucocytes across the endothelium across the BBB
 - 3) **Fingolimod:**
 - ✓ Sphingosine 1-phosphate receptor modulator,
 - ✓ Prevents lymphocytes from leaving lymph nodes.
 - ✓ An **oral** formulation is available
- ☒ **Mitoxantrone:** reserved for high frequency relapse rates unresponsive to beta-interferon
- ☒ **Plasma exchange** has a place in severe function or life threatening relapses not responding to conventional treatment.

Some specific problems:

Spasticity:

- **Baclofen** and **gabapentin** are **first-line**.
- Other options include **diazepam**, **dantrolene** and **tizanidine**
- physiotherapy is important
- cannabis and botox are undergoing evaluation

Bladder dysfunction:

- may take the form of urgency, incontinence, overflow etc
- guidelines stress the importance of getting an ultrasound first to assess bladder emptying - anticholinergics may worsen symptoms in some patients
 - ☒ **if significant residual volume** ⇒ intermittent **self-catheterisation**
 - ☒ **if no significant residual volume** ⇒ **anticholinergics** may improve urinary frequency

Multiple sclerosis good prognostic features

- female sex, young age of onset
- relapsing-remitting disease
- sensory symptoms
- long interval between first two relapses

Ways of remembering prognostic features

- the typical patient carries a better prognosis than an atypical presentation

Baclofen toxicity:

Onset of toxicity is rapid and its effect can last up to 35-40 hours post ingestion.

Features include:

- 1) Drowsiness, Coma
- 2) Respiratory depression
- 3) Hypotonia, Hyporeflexia
- 4) Hypothermia and Hypotension.
- 5) Bradycardia with first degree heart block and prolongation of Q-T interval can occur

Treatment is usually supportive and often requires intensive care.

Benign paroxysmal positional vertigo

(BPPV)

- BPPV is one of the most common causes of vertigo encountered.
- **It is characterized by:**
 - ☒ The sudden onset of dizziness and vertigo
 - ☒ Triggered by changes in head position.
- The average age of onset is **55 years** and it is less common in younger patients.

Features:

- 1) vertigo triggered by change in head position (e.g. rolling over in bed or gazing upwards)
- 2) Symptoms are usually most severe in the lateral decubitus position with the affected ear down.
- 3) ~~Hearing loss~~ is **not a feature**.
- 4) may be associated with nausea
- 5) each episode typically lasts 10-20 seconds
- 6) Positive **Dix-Hallpike manoeuvre**:
 - ☒ The vertigo can be reproduced by turning the head of the patient 45 degrees to the right and then taking the patient to the supine position.
 - ☒ There is nystagmus (upbeating and torsional), which last only a few seconds.
(https://www.youtube.com/watch?v=RNBjLed_Slc)
- 7) BPPV has a **good prognosis** and usually resolves spontaneously after a few weeks to months.

Symptomatic relief may be gained by:

- 1) **Epley manoeuvre** (successful in around 80% of cases)
See this link <https://www.youtube.com/watch?v=ZqokxZRbJfw>
 - 2) **teaching the patient exercises** they can do themselves at home, for example Brandt-Daroff exercises
 - 3) Medication is often prescribed (e.g. **Betahistine**) but it tends to be of **limited value**.
- **Benign positional vertigo (BPV)** is characterised by brief episodes of severe vertigo accompanied by nausea and vomiting. Symptoms are usually most severe in the lateral decubitus position with the affected ear down.
 - Episodic vertigo usually lasts for several weeks and then resolves spontaneously. Hearing loss is not a feature.
 - In contrast to positional nystagmus from a central cause, the nystagmus in BPV exhibits latency, **fatigue and habituation**.
 - Both central (eg, brainstem or cerebellum) and peripheral vestibular lesions can cause positional nystagmus and vertigo. **Central positional nystagmus** is usually **static**, in that the nystagmus persists as long as the head is kept in the provoking position.
 - **Positional vertigo due to peripheral vestibular pathology** is always **transient**.
 - Observations of the direction of nystagmus, as well as features of latency and fatigability, can help confirm a peripheral localization and make imaging unnecessary.

Tinnitus

Causes of tinnitus include:

Meniere's disease	• Associated with hearing loss, • vertigo, • tinnitus and sensation of fullness or pressure in one or both ears
Acoustic neuroma	• Hearing loss, • vertigo, tinnitus • Absent corneal reflex is important sign (cranial nerve V) • Associated with neurofibromatosis type 2 (bilateral)
Otosclerosis	• Onset is usually at 20-40 years • Positive FH • Conductive deafness • Tinnitus • Normal tympanic membrane* *10% of patients may have a 'flamingo tinge', caused by hyperaemia
Hearing loss	Causes include excessive loud noise and presbycusis (age-related <u>sensorineural hearing loss</u> .)
Drugs	• Aspirin • Loop diuretics • Aminoglycosides • Quinine

Other causes include

- 1) impacted ear wax
- 2) chronic suppurative otitis media

Meniere's disease

- A disorder of the **inner ear** of unknown cause.
- Characterized by **excessive pressure** and **progressive dilation** of the endolymphatic system.
- It is more common in **middle-aged** adults but may be seen at any age.
- Meniere's disease has a similar prevalence in both men and women.

Features:

- 1) Recurrent episodes of **vertigo**, **tinnitus** and **hearing loss** (sensorineural).
- 2) Vertigo is usually the prominent symptom
- 3) a sensation of aural fullness or pressure is now recognized as being common
- 4) other features include nystagmus and a positive Romberg test
- 5) episodes last minutes to hours
- 6) typically symptoms are unilateral but bilateral symptoms may develop after a number of years

Natural history:

- symptoms resolve in the majority of patients after 5-10 years
- the majority of patients will be left with a degree of hearing loss
- psychological distress is common

Management:

- ☒ ENT assessment is required to confirm the diagnosis
- ☒ Patients should inform the DVLA. The current advice is to cease driving until satisfactory control of symptoms is achieved
- ☒ Acute attacks:
 - ✓ Buccal or intramuscular **prochlorperazine**
 - ✓ Admission is sometimes required
- ☒ Prevention: **betahistine** may be of benefit

Prochlorperazine: dopamine (D2) receptor antagonist that belongs to the **phenothiazine** class of antipsychotics that are used **antiemetic** of **nausea** and **vertigo**. It is also a highly potent **typical antipsychotic**, 10–20× more potent than **chlorpromazine**. It is also used to treat migraine.

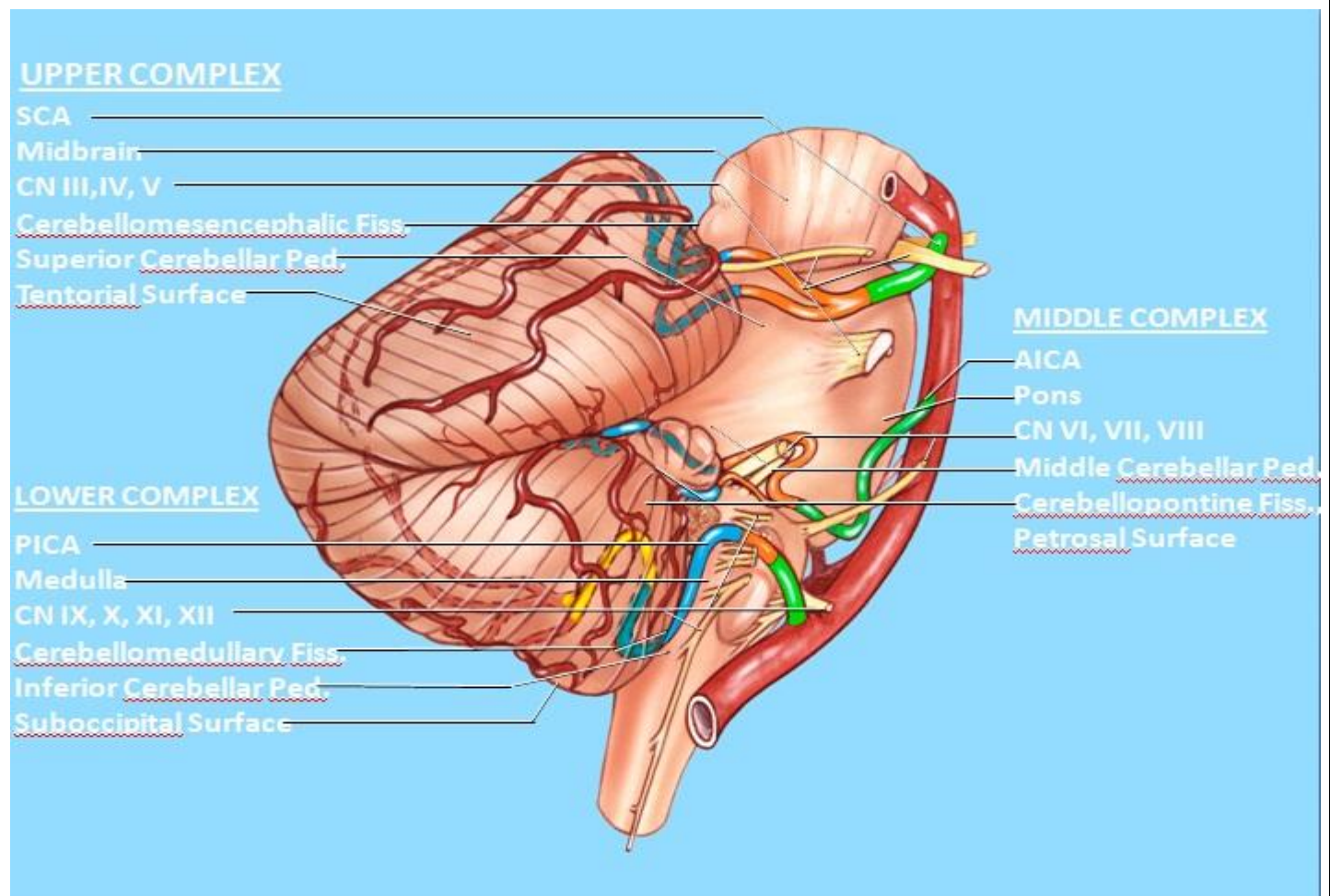
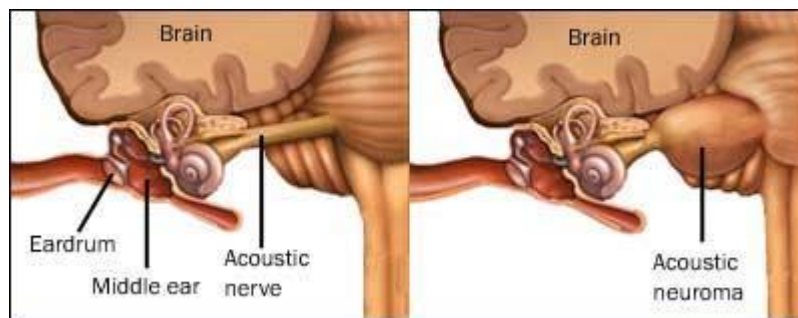
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Acoustic neuromas

- Acoustic neuromas (more correctly called vestibular schwannomas)
- Account for approximately:
 - ✓ 5% of intracranial tumors and
 - ✓ 90% of cerebellopontine angle

Features can be predicted by the affected cranial nerves: 5, 7 & 8

- ☒ **cranial nerve V:** → absent corneal reflex
 - ☒ **cranial nerve VII:** → facial palsy
 - ☒ **cranial nerve VIII:** → hearing loss, vertigo, tinnitus
- **Bilateral** acoustic neuromas are seen in **neurofibromatosis type 2**
 - **MRI** of the cerebellopontine angle is the investigation of choice



Rinne's and Weber's test

Performing both Rinne's and Weber's test allows differentiation of conductive and sensorineural deafness.

Rinne's test:

- tuning fork is placed over the mastoid process until the sound is no longer heard, followed by repositioning just over external acoustic meatus
 - ☒ air conduction (AC) is normally better than bone conduction (BC)
 - ☒ if BC > AC then **conductive deafness**

Weber's test:

- tuning fork is placed in the middle of the forehead equidistant from the patient's ears
- the patient is then asked which side is loudest
 - ☒ in unilateral sensorineural deafness, sound is localised to the unaffected side
 - ☒ in unilateral conductive deafness, sound is localised to the affected side

Romberg's test

Positive in conditions causing **sensory ataxia** such as:

- 1) Vitamin deficiencies such as Vitamin B₁₂
 - 2) Conditions affecting the dorsal columns of the spinal cord, such as **tabes dorsalis** (**neurosyphilis**)
 - 3) Conditions affecting the sensory nerves (sensory peripheral neuropathies), such as chronic inflammatory **demyelinating** polyradiculoneuropathy (**CIDP**).
 - 4) Friedreich's ataxia
 - 5) Ménière's disease
-
- ☒ Romberg's test is a test of the **proprioception receptors** and **pathways function**.
 - ☒ Romberg's test is **not a test of cerebellar function**.
 - ☒ Patients with **cerebellar ataxia** will be unable to balance even with the eyes open, therefore, the test cannot proceed beyond the first step and no patient with cerebellar ataxia can correctly be described as Romberg's positive. Rather,
 - ☒ A positive Romberg's test has been shown to be 90% sensitive for **lumbar spinal stenosis**.

Idiopathic intracranial hypertension

- Pseudotumour cerebri and formerly benign intracranial hypertension
- a condition classically seen in young, overweight females

Features:

- 1) headache
- 2) **blurred vision**
- 3) **papilloedema** (usually present)
- 4) enlarged blind spot
- 5) sixth nerve palsy may be present

Risk factors:

- 1) obesity
- 2) female sex
- 3) pregnancy
- 4) drugs:
 - ✓ oral contraceptive pill, steroids,
 - ✓ Treatments for acne (tetracycline, nitrofurantoin, retinoids)
 - ✓ vitamin A (Hypervitaminosis A)

*if intracranial hypertension is thought to occur secondary to a known causes (e.g. Medication) then it is of course not idiopathic

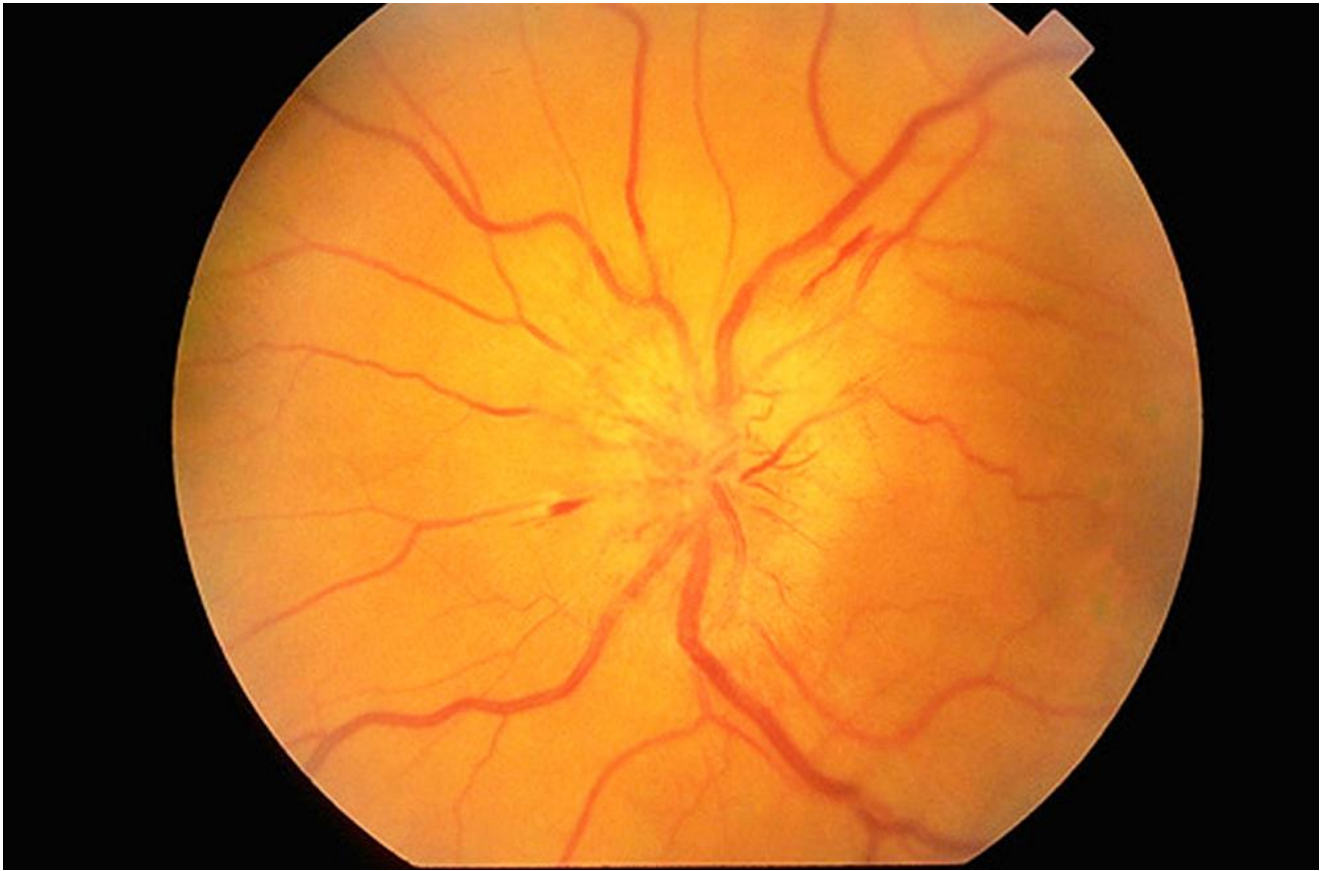
Investigations:

- ☒ CT scan is often **normal**;
- ☒ The diagnosis is confirmed by finding an **elevated cerebrospinal fluid opening pressure (more than 20 cmH₂O)**.
- ☒ CSF protein, glucose and cell count will be **normal**.
- ☒ The differential diagnosis includes **venous sinus thrombosis**; increased use of MRI has shown that small thromboses are commoner than previously thought in these patients. **MRI and/or MRI venography** is essential in these patients.

Management:

- 1) weight loss
 - 2) diuretics e.g. **acetazolamide**
 - 3) repeated lumbar puncture
 - 4) Surgery:
 - ☒ **A lumboperitoneal or ventriculoperitoneal shunt** may also be performed to reduce intracranial pressure
 - ☒ **Optic nerve sheath decompression and fenestration** may be needed to prevent damage to the optic nerve.
- ☒ Visual loss is the single threatening complication of idiopathic intracranial hypertension (IIH).
 - Urgent lumboperitoneal shunt is the treatment of choice.
 - Optic nerve fenestration is an alternative.

There are no comparative studies between the two interventions.



The slide shows papilloedema

Headache

Medication overuse headache:

- One of the most common causes of chronic daily headache.
- It may affect up to 1 in 50 people

Features:

- 1) present for 15 days or more per month
- 2) developed or worsened whilst taking regular symptomatic medication
- 3) patients using opioids and triptans are at most risk
- 4) may be psychiatric co-morbidity

Management: (from 2008 SIGN guidelines)

- ☒ simple analgesics and triptans should be withdrawn abruptly (may initially worsen headaches)
- ☒ opioid analgesics should be gradually withdrawn

Migraine

Migraine without aura

The International Headache Society has produced the following diagnostic criteria for migraine without aura:

Point	Criteria
A	At least 5 attacks fulfilling criteria B-D
B	Headache attacks lasting 4-72 hours* (untreated or unsuccessfully treated)
C	Headache has at least two of the following characteristics: 1. unilateral location* 2. pulsating quality (i.e., varying with the heartbeat) 3. moderate or severe pain intensity 4. aggravation by/or causing avoidance of routine physical activity (e.g. walking or climbing stairs)
D	During headache at least one of the following: 1. nausea and/or vomiting* 2. photophobia and phonophobia
E	Not attributed to another disorder (history and examination do not suggest a secondary headache disorder or, if they do, it is ruled out by appropriate investigations or headache attacks do not occur for the first time in close temporal relation to the other disorder)

*In children, attacks may be shorter-lasting, headache is more commonly bilateral, and gastrointestinal disturbance is more prominent.

Migraine with aura

- Seen in around **25%** of migraine patients
- Tends to be easier to diagnose with a typical aura being progressive in nature and may occur hours prior to the headache. Dizziness and fatigue
- **Typical aura include:**
 - a transient hemianopic disturbance or
 - A spreading scintillating scotoma ('jagged crescent'). ضوء لامع SSS متالق..... هلال خشن
 - **Tunnel vision**, zigzag lines or stars. النجوم فى عز الظهر
 - Sensory symptoms may also occur

If we compare these guidelines to the NICE criteria the following points are noted:

- NICE suggests migraines may be unilateral or bilateral
- NICE also give more detail about **typical auras**:
 - Auras may occur with or without headache and:
 - are **fully reversible**
 - develop over at least 5 minutes
 - last 5-60 minutes

The following aura symptoms are **atypical** and may prompt further investigation/referral:

- 1) Decreased level of consciousness.
- 2) motor weakness
- 3) poor balance
- 4) double vision
- 5) visual symptoms affecting only one eye

Migraine management

- **It should be noted that as a general rule:**

- ☒ 5-HT receptor **agonists** are used in the **acute treatment** of migraine whilst
- ☒ 5-HT receptor **antagonists** are used in **prophylaxis**.

NICE produced guidelines in 2012 on the management of headache, including migraines.

Acute treatment:

- 1) **First-line:** offer **combination** therapy with:
 - an **oral triptan** and **NSAID**, or
 - an **oral triptan** and **paracetamol**
 - for young people aged **12-17 years** consider a **nasal triptan** in preference to an oral triptan
- 2) if the above measures are not effective or not tolerated:
 - Offer a **non-oral preparation** of **metoclopramide*** or **prochlorperazine** and
 - consider adding a **non-oral NSAID** or **triptan**

*caution should be exercised with young patients as **acute dystonic reactions (extrapyramidal)** may develop with metoclopramide

Prophylaxis:

- ☒ Prophylaxis should be given if patients are experiencing **2 or more attacks per month**.
- ☒ Modern treatment is effective in about 60% of patients.
- ☒ NICE advise either:
 - ⇒ **Topiramate** or
 - ⇒ **Propranolol** 'according to the person's preference, co morbidities and risk of adverse events'.
- ☒ **Propranolol** should be used in preference to **topiramate** in women of child bearing age as it may be **teratogenic** and it can **reduce the effectiveness of hormonal contraceptives**
- ☒ If these measures fail NICE recommend:
 - 1) a course of up to **10 sessions** of **acupuncture** over **5-8 weeks'** or
 - 2) **gabapentin**
 - 3) **riboflavin 400 mg** once a day may be effective in reducing migraine frequency and intensity
 - 4) For women with predictable **menstrual migraine** treatment NICE recommend either:
 - **Frovatriptan** (2.5 mg twice a day) or
 - **Zolmitriptan** (Zomig)(2.5 mg twice or three times/day) as a type of 'mini-prophylaxis'
- ☒ **Pizotifen** is no longer recommended. Adverse effects such as weight gain & drowsiness are common

Topiramate is associated with:

- Renal stones
- Weight loss
- Cognitive impairment
- Tingling in extremities.

To summarize

- Sumatriptan is structurally similar to serotonin, and is a 5-HT₁ agonist.
- Acute treatment: oral triptan + an NSAID, or an oral triptan + paracetamol
- (for young 12-17 years---> a nasal triptan)
- if not effective or not tolerated offer a non-oral preparation of metoclopramide* or prochlorperazine + a non-oral NSAID or triptan
- Prophylaxis: - either topiramate or propranolol
- 10 sessions of acupuncture over 5-8 weeks' or gabapentin
- riboflavin (400 mg once a day)
- predictable menstrual migraine frovatriptan (2.5 mg bd) or zolmitriptan (2.5 mg bd or tds) as 'mini-prophylaxis'

Migraine: pregnancy, contraception and other hormonal factors

SIGN produced guidelines in 2008 on the management of migraine, the following is selected highlights:

Migraine during pregnancy

- **paracetamol 1g** is first-line
- **aspirin 300mg** or **ibuprofen 400mg** can be used second-line in the first and second trimester

Migraine and the combined oral contraceptive (COC) pill

If patients have **migraine with aura** then the **COC is absolutely contraindicated** due to an **increased risk of stroke** (RR 8.72)

Migraine and hormone replacement therapy (HRT)

- safe to prescribe HRT for patients with a history of migraine but it **may make migraines worse**

Migraine and menstruation

- many women find that the frequency and severity of migraines increase around the time of menstruation
- **SIGN recommends that women are treated with:**
 - ☒ mefenamic acid or
 - ☒ A combination of aspirin, paracetamol and caffeine.
 - ☒ Triptans are also recommended in the acute situation

Triptans

- Triptans are specific **5-HT₁ agonists** producing vasoconstriction used in the acute treatment of migraine.
- They are generally used first-line in combination therapy with an NSAID or paracetamol.

Prescribing points:

- ☒ should be taken as soon as possible **after the onset of headache**, rather than at onset of aura
- ☒ oral, orodispersible, nasal spray and subcutaneous injections are available

Adverse effects:

- ☒ **'triptan sensations'**: tingling, heat, tightness (e.g. throat and chest), heaviness, pressure

Contraindications:

- ☒ patients with a history of, or significant risk factors for, **ischemic heart disease** or **cerebrovascular disease**

Cluster headache

Cluster headaches* are more common in **men** (9:1) and **smokers**.

Features:

- 1) pain typical occurs **once** or **twice** a day, each episode lasting **15 mins - 2 hours**
- 2) Clusters typically last 4-12 weeks with each cluster occurring several times yearly.
- 3) intense pain around one eye (recurrent attacks 'always' affect same side)
- 4) patient is restless during an attack
- 5) accompanied by redness, lacrimation, lid swelling
- 6) nasal stuffiness انسداد الأنف
- 7) miosis and ptosis in a minority (post ganglionic Horner Synd)---**transient**
- 8) The attacks often are **nocturnal** and associated with **parasympathetic** over activity

Management:

☒ **acute:**

- 1) 100% oxygen,
- 2) SC or a nasal triptan

☒ **prophylaxis:** ⇒ **verapamil**, **prednisolone**, sodium valproate, lithium, ergotamine

☒ NICE recommend seeking specialist advice from a neurologist if a patient develops cluster headaches with respect to neuroimaging

Chronic paroxysmal hemicrania

- It has features of cluster headaches but is associated with attacks of **shorter duration** and **increased frequency**.
- Each headache can last between 3-45 minutes and occur 20-40 times per day.
- Chronic paroxysmal hemicrania almost invariably responds to **indomethacin**.

*some neurologists use the term trigeminal autonomic cephalgia to group a number of conditions including cluster headache, paroxysmal hemicrania and short-lived unilateral neuralgiform headache with conjunctival injection and tearing (SUNCT). It is recommended such patients are referred for specialist assessment as specific treatment may be required, for example it is known paroxysmal hemicrania responds very well to indomethacin

Cluster headache: Episodic eye pain, lacrimation, nasal stuffiness daily

Cluster headache ----> post ganglionic Horner Synd. تذكر

Triptan: agonist effects on serotonin 5-HT_{1B} and 5-HT_{1D} receptors in cranial blood vessels (causing their **constriction**) and subsequent inhibition of pro-inflammatory neuropeptide release.

Post-lumbar puncture headache

- Headache following lumbar puncture (LP) occurs in approximately one-third of patients.
- The pathophysiology of is unclear but **may relate to a 'leak' of CSF following dural puncture.**
- Post-LP headaches are more common in **young females** with a **low body mass index**

Typical features:

- 1) usually develops within 24-48 hours following LP but may occur up to one week later
- 2) may last several days
- 3) worsens with upright position
- 4) improves with recumbent position

Factors which may contribute to headache	Factors which do not contribute to headache
Increased needle size Direction of bevel Not replacing the stylet Increased number of LP attempts	Opening pressure of CSF Increased volume of CSF removed Increased fluid intake post procedure Bed rest following procedure Position of patient

Management:

- ☒ supportive initially (analgesia, rest)
- ☒ if pain continues for more than 72 hours then specific treatment is indicated, to prevent subdural haematoma

☒ Treatment options include:

- 1) blood patch,
- 2) epidural saline and
- 3) intravenous caffeine

Acute confusional state

- Also known as **delirium** or acute organic brain syndrome.
- It affects up to 30% of elderly patients admitted to hospital.

Features: wide variety of presentations

- 1) poor attention
- 2) disorientation
- 3) memory disturbances (loss of short term > long term)
- 4) mood change
- 5) may be very agitated or withdrawn
- 6) visual hallucinations
- 7) disturbed sleep cycle

Management:

- 1) treatment of underlying cause
- 2) modification of environment
- 3) the 2006 Royal College of Physicians publication 'The prevention, diagnosis and management of delirium in older people: concise guidelines' recommended **haloperidol 0.5 mg** as **the first-line sedative**
- 4) the 2010 NICE delirium guidelines advocate the use of **haloperidol** or **olanzapine**

Transient global amnesia (TGA)

- Most attacks last one to eight hours with a mean duration of 4.2 hours.
- Patients are disoriented to time and place with 60% to 90% exhibiting repetitive questioning, "**Where am I?**" which may last throughout the attack.
- The precise pathophysiology of TGA is not clear.
- On positron emission tomography (PET) and diffusion-weighted MRI (DWI), blood flow to specific brain areas that involve memory appears to be disrupted transiently during TGA. This includes the thalamus and/or mesial temporal structures (in particular the amygdala and hippocampus).

Neurodegenerative Diseases

Dementia

- Dementia is thought to affect over 700,000 people in the UK and accounts for a large amount of health and social care spending.
- The most common cause of dementia in the UK is Alzheimer's disease followed by vascular and Lewy body dementia. These conditions may coexist.

Features:

- diagnosis can be difficult and is often delayed
- The mini-mental state examination is widely used. A score of ≤ 24 out of 30 suggests dementia

Causes:

Common causes:

- **Alzheimer's disease**
- **CVD: multi-infarct dementia** (c. 10-20%)
- **Lewy body dementia** (c. 10-20%)

Rarer causes (c. 5% of cases)

- **Huntington's** (progressive dementia and chorea appear between 30 -50 years age)
- **CJD**
- **Pick's disease** (atrophy of frontal and temporal lobes)
- **HIV** (50% of AIDS patients)

Important differentials: potentially treatable

- hypothyroidism, Addison's, B12/folate/thiamine deficiency
- normal pressure hydrocephalus, subdural haematoma, brain tumour, syphilis
- depression
- chronic drug use e.g. Alcohol, barbiturates

Management:

- ☒ In **primary care** a **blood screen** is usually sent to exclude reversible causes (e.g. Hypothyroidism)
 - ⇒ NICE recommend the following tests: FBC, U&E, LFTs, calcium, glucose, TFTs, vitamin B12 and folate levels.
- ☒ Patients are now commonly referred on to old-age psychiatrists (sometimes working in 'memory clinics').
- ☒ in **secondary care** **neuroimaging** is performed* to exclude other reversible conditions (e.g. Subdural haematoma, normal pressure hydrocephalus) and help provide information on aetiology to guide prognosis and management

*in the 2011 NICE guidelines structural imaging was said to be essential in the investigation of dementia

Alzheimer's disease

- A progressive degenerative disease of the brain
- accounting for the majority of dementia seen in the UK

Genetics:

- most cases are sporadic
- 5% of cases are inherited as an autosomal dominant trait
- mutations in:
 - ☒ the amyloid precursor protein (chromosome 21),
 - ☒ presenilin 1 (chromosome 14) and
 - ☒ presenilin 2 (chromosome 1) genes are thought to cause the inherited form
- apoprotein E allele E4 - encodes a cholesterol transport protein

Pathological changes:

- 1) **macroscopic:** widespread cerebral atrophy, particularly involving the cortex and hippocampus
- 2) **microscopic:**
 - Cortical plaques:** Due to deposition of:
 - 1) type A-Beta-amyloid protein and
 - 2) intraneuronal neurofibrillary tangles caused by abnormal aggregation of the tau protein
- 3) **biochemical:**
 - ✓ There is a deficit of acetylcholine from damage to an ascending forebrain projection

Management:

NICE guidelines on Alzheimer's disease and the pharmacological management of dementia suggest the following:

- 1) **Acetylcholinesterase inhibitors:**

NICE now recommend (donepezil, galantamine and rivastigmine) as options for managing mild to moderate Alzheimer's disease
 - 2) **Memantine:** a NMDA receptor antagonist

Recommended as an option for managing Alzheimer's disease for people with:

 - ☒ moderate Alzheimer's disease who are intolerant of or have a contraindication to AChE inhibitors, or
 - ☒ Severe Alzheimer's disease.
- ☒ NICE guidelines recommend discontinuation of cholinesterase inhibitors once the mini mental state examination has fallen below 12.
 - ☒ Consider switch to memantine, which is licensed for use in moderate to severe dementia. The new NICE draft guidelines, however, do not recommend its use because of lack of cost effectiveness.

- Repeating the cognitive assessment every 6 months assesses benefit.
- Up to half the patients given these drugs will show a slower rate of cognitive decline.
- The drug should be discontinued in those thought not to be responding.
- In those who are responding, drugs should be stopped once the MMSE score is less than 10.

Neurofibrillary tangles:

- paired helical filaments are partly made from a protein called tau
- in AD: tau proteins are excessively phosphorylated

Lewy body dementia

- an increasingly recognized cause of dementia,
- Accounting for **up to 20% of cases**.
- The characteristic pathological feature is **alpha-synuclein cytoplasmic inclusions** (Lewy bodies) in the **substantia nigra**, **paralimbic** and **neocortical** areas
- The relationship between Parkinson's disease and Lewy body dementia is complicated, particularly as dementia is often seen in Parkinson's disease.
- Also, up to 40% of patients with Alzheimer's have Lewy bodies
- **Neuroleptics should be avoided** in Lewy body dementia as patients are extremely sensitive and may **develop irreversible Parkinsonism**.
- Questions may give a history of a patient who has deteriorated following the introduction of an antipsychotic agent

Features: Dementia+ Parkinsonism+ Visual hallucinations

- 1) progressive cognitive impairment
- 2) parkinsonism
- 3) visual hallucinations (delusions and non-visual hallucinations may also be seen)

Diagnosis:

- ☒ usually clinical
- ☒ **Single-photon emission computed tomography (SPECT)** is increasingly used.
 - ✓ It is currently commercially known as a DaTscan.
 - ✓ Dopaminergic iodine-123-radiolabelled 2-carbomethoxy-3-(4-iodophenyl)-N-(3-fluoropropyl) nortropane (123-I FP-CIT) is used as the radioisotope.
 - ✓ The **sensitivity** of **SPECT** in diagnosing Lewy body dementia is **90%**, **specificity 100%**

Management: Rivastigmine:

The treatment of choice as improves both the visual hallucinations, and cognitive impairment.

Frontotemporal dementia (Pick's disease)

- A rare form of dementia characterised by degeneration of the frontal and temporal lobes.
- More common under 65 years.
- It presents with changes in behaviour and loss of insight more commonly than memory problems.
- Patients are disinhibited, apathetic and can be compulsive overeaters.
- They may have a normal MMSE, visuospatial and language function but **they fail on tasks of verbal fluency** and **executive function**
- Presentations are of frontal or temporal lobe syndromes, depending on the location of maximal lobar atrophy.
 - ☒ Patients with frontal atrophy present with early personality change.
 - ☒ Predominant temporal lobe atrophy is associated with aphasia and semantic memory impairment.

Pathologically:

- ☒ Pick's disease is associated with Pick bodies which are argyrophilic inclusion bodies within the neuronal cytoplasm.
- ☒ EEG is relatively normal by contrast with Alzheimer's disease.

Creutzfeldt-Jakob disease

- CJD is at times called a human form of mad cow disease (bovine spongiform encephalopathy or BSE) جنون البقر....او المخ الاسفنجي
- CJD is rapidly progressive neurological condition caused by **prion proteins**
- Prions are proteins that occur normally in neurons of the CNS. These proteins affect signaling processes ⇒ damaging neurons ⇒ degeneration ⇒ spongiform appearance in the affected brain.
- These proteins induce the formation of amyloid folds resulting in tightly packed beta-pleated sheets resistant to proteases.

Features:

- 1) Dementia (rapid onset) ديمنشيا سريعة وميوكلونوس وatakسيا.....تميز جنون البقر
- 2) Myoclonus
- 3) Ataxia

Investigation:

- 1) CSF is usually **normal**
- 2) EEG: biphasic or **triphasic periodic sharp wave complexes**, **high amplitude** (only in sporadic CJD)
- 3) MRI: hyperintense signals in the **BG** and **thalamus**

Sporadic CJD:

- accounts for **85%** of cases
- mean age of onset is **65** years

Familial **10-15%** of cases

Variant CJD:

Rapid cognitive decline in a young person with myoclonus is strongly suggestive of CJD thought to be caused by consumption of food contaminated with prions (which also cause BSE)

- younger patients (average age of onset = 25 years)
- psychological symptoms such as anxiety, withdrawal and dysphonia are the most common presenting features
- the 'prion protein' is encoded on chromosome 20 - it's role is not yet understood
- methionine homozygosity at codon 129 of the prion protein is a risk factor for developing CJD
- all patients who have so far died have had this
- median survival = **13 months**

Iatrogenic:

This form of CJD arises from contamination with tissue from an infected person, usually as the result of a medical procedure e.g. blood transfusion from the infected person, use of human-derived pituitary growth hormones, gonadotropin hormone therapy, corneal and/or meningeal transplants

CJD is incurable and invariably fatal disease

Other prion diseases

- kuru
- fatal familial insomnia
- Gerstmann Straussler-Scheinker disease

Normal pressure hydrocephalus

- A reversible cause of dementia seen in elderly patients.
- It is thought to be secondary to reduced CSF absorption at the arachnoid villi.
- These changes may be secondary to head injury, subarachnoid hemorrhage or meningitis
- A classical triad of features is seen:
 - ✓ dementia and bradyphrenia
 - ✓ gait abnormality (may be similar to Parkinson's disease)
 - ✓ urinary incontinence

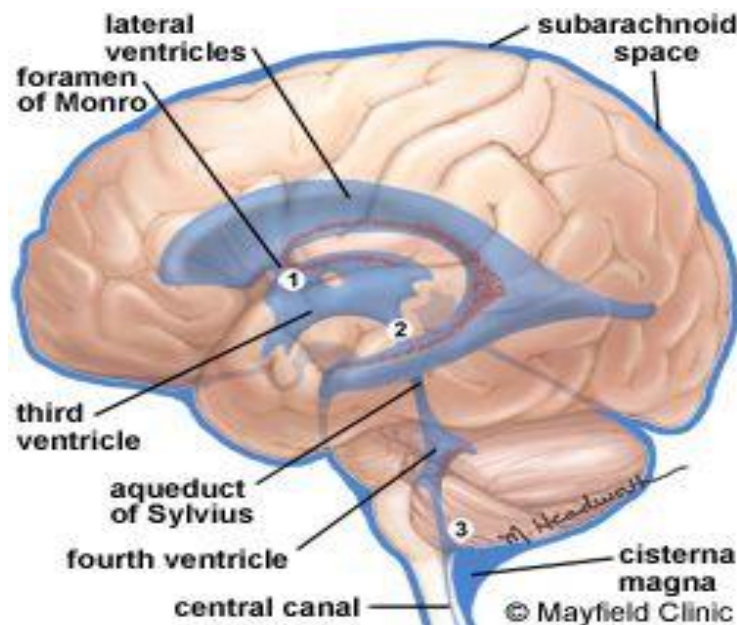
Imaging:

- hydrocephalus with enlarged ventricles

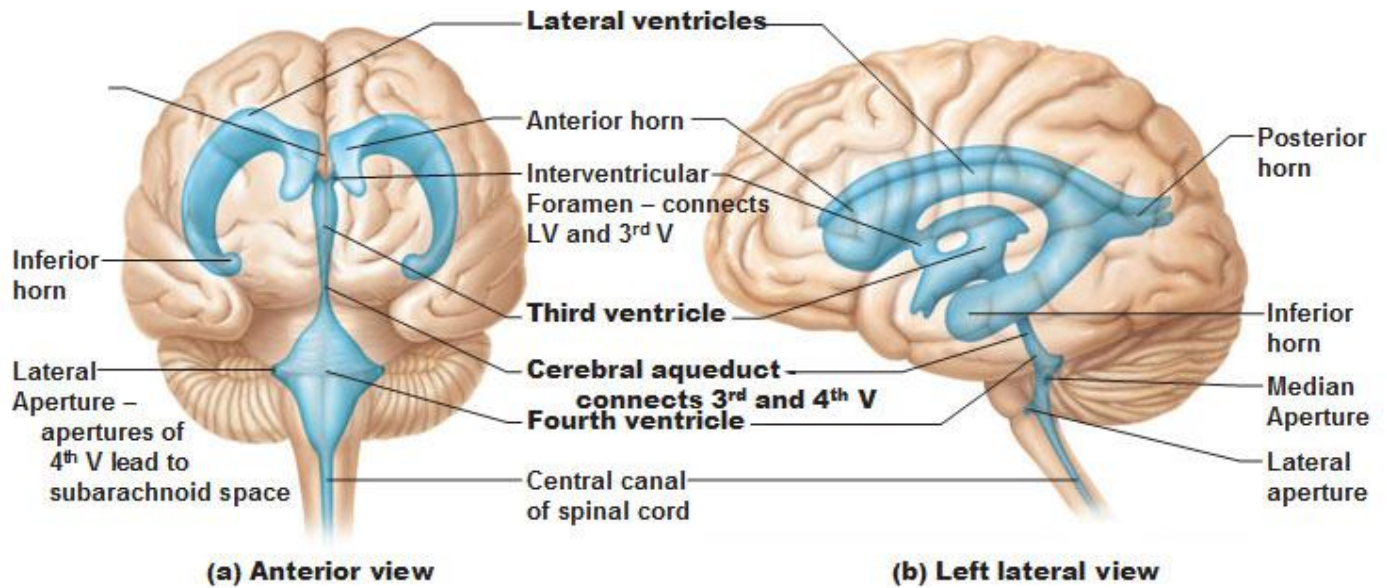
Management:

- ventriculoperitoneal shunting
 - In equivocal cases therapeutic CSF drainage via lumbar puncture is performed to identify the patients likely to benefit from permanent drainage
- bradyphrenia: slow thinking
 - Normal pressure hydrocephalus is a reversible cause of dementia in elderly.

Normal pressure hydrocephalus-----> No Papilledema.....هام جدا



Ventricles of the Brain



Neurodegenerative Diseases

Motor neuron disease

Features:

- Motor neuron disease is a neurological condition of unknown cause.
- Can present with both upper and lower motor neuron signs.
- It rarely presents before 40 years
- various patterns of disease are recognized including
 - 1) amyotrophic lateral sclerosis,
 - 2) primary lateral sclerosis,
 - 3) progressive muscular atrophy,
 - 4) Progressive bulbar palsy.
- In some patients however, there is a combination of clinical patterns

There are a number of clues which point towards a diagnosis of motor neuron disease:

- 1) fasciculation
- 2) absence of sensory signs/symptoms* (purely motor)
- 3) LMN signs in arms and UMN signs in legs
- 4) wasting of the small hand muscles & tibialis anterior is common

*vague sensory symptoms may occur early in the disease (e.g. limb pain) but 'never' sensory signs

Other features:

- 1) doesn't affect external ocular muscles
- 2) no cerebellar signs
- 3) abdominal reflexes are usually preserved
- 4) sphincter dysfunction if present is a late feature

Diagnosis:

- The diagnosis of motor neuron disease is clinical
- nerve conduction studies show normal motor conduction and can help exclude a neuropathy
- Electromyography shows a reduced number of action potentials with increased amplitude.
- MRI: usually performed to exclude the differential diagnosis of cervical cord compression and myelopathy

Motor neuron disease types:

Amyotrophic lateral sclerosis (50% of patients)

- typically LMN signs in arms
- and UMN signs in legs
- in familial cases the gene responsible lies on chromosome 21 and codes for **superoxide dismutase**

Primary lateral sclerosis:

- UMN signs only

Progressive muscular atrophy:

- LMN signs only
- affects distal muscles before proximal
- carries best prognosis

Progressive bulbar palsy

- palsy of the tongue, muscles of chewing/swallowing and facial muscles due to loss of function of brainstem motor nuclei
- carries worst prognosis

Motor neuron disease management:

A) **Riluzole:**

- prevents stimulation of glutamate receptors
- used mainly in amyotrophic lateral sclerosis
- prolongs life by about **3 months**

B) **Respiratory care:**

- non-invasive ventilation (usually **BIPAP**) is used at night
- studies have shown a survival benefit of around 7 months

Prognosis:

- poor: 50% of patients die within 3 years

Multifocal motor neuropathy (MMN):

- autoimmune neuropathy associated in 80% of cases with an elevated anti-GM1 ganglioside antibody and typically presents with progressive weakness affecting an isolated limb without sensory involvement
- Rarely there is cranial nerve or respiratory involvement.
- There is persistent motor conduction block of the innervating nerves and depressed reflexes
- It is an important differential diagnosis of motor neurone disease as it is potentially treatable.
- Treatment with IV immunoglobulin may be very effective in some patients.
- Cyclophosphamide is also used on a long term basis.

Cerebellar syndrome

Unilateral cerebellar lesions cause-----> ipsilateral signs

Causes:

- 1) Friedreich's ataxia, ataxic telangiectasia
- 2) cerebellar haemangioma
- 3) stroke
- 4) alcohol
- 5) multiple sclerosis (relapse usually)
- 6) hypothyroidism
- 7) phenytoin, lead poisoning
- 8) paraneoplastic e.g. secondary to lung cancer

Friedreich's ataxia

- the most common of the **early-onset** hereditary ataxias
- It is an **autosomal recessive**, **trinucleotide repeat disorder** characterised by a **GAA** repeat in the X25 gene on chromosome 9 (frataxin).
- Friedreich's ataxia is unusual amongst trinucleotide repeat disorders in **not demonstrating the phenomenon of anticipation**.
- The typical age of onset is **10-15 years** old.
- **Gait ataxia** and **kyphoscoliosis** are the most common presenting features.
- **The posterior columns**, **spinocerebellar** and **corticospinal tracts** are affected leading to **cerebellum dysfunction**, **spastic paraparesis** and **absent reflexes** in lower limbs.

Neurological features:

- 1) absent ankle jerks/extensor plantars (**LMN + UMN signs**)
- 2) cerebellar ataxia
- 3) **optic atrophy**
- 4) spinocerebellar tract degeneration
- 5) kyphoscoliosis, pes cavus

Other features:

- 1) hypertrophic obstructive cardiomyopathy **HOCM** (90%, most common cause of death)
- 2) **Diabetes mellitus** (10-20%)
- 3) **high-arched palate**

Ataxic telangiectasia

- An **autosomal recessive** disorder
- Caused by a defect in the ATM gene which encodes for DNA repair enzymes.
- It is one of the inherited **combined immunodeficiency** disorders.
- It typical presents in early childhood with abnormal movements (**chorea**).

Features:

- 1) cerebellar ataxia
- 2) telangiectasia (spider angiomas)
- 3) IgA deficiency resulting in recurrent chest infections
- 4) 10% risk of developing malignancy, lymphoma or leukaemia, but also non-lymphoid tumors

Lateral medullary syndrome

- Also known as **Wallenberg's syndrome**,
- occurs following occlusion of the **posterior inferior cerebellar artery(PICA)**

Ipsilateral Cerebellar features:

- 1) ataxia
- 2) nystagmus

Brainstem features:

- Ipsilateral:
 - 1) facial numbness, (spinal trigeminal nucleus & tract)
 - 2) Dysphagia (nucleus ambiguus - ----vagus nerve and glossopharyngeal nerve)),
 - 3) vestibular nuclei-----vomiting, vertigo, nystagmus
 - 4) sympathetic fibers e.g. Horner's
- Contralateral: limb/torso sensory loss (pain & temperature loss) ----lateral spinothalamic tract
- There is a loss of pain and temperature sensation on the contralateral (opposite) side of the body and ipsilateral (same) side of the face. This crossed finding is diagnostic for the syndrome.

كل المشاكل على نفس الناحية..... عدا الاحساس فى الاطراف والجذع

Movement Disorders

Tremor

The table below lists the main characteristics of the most important causes of tremor

Parkinsonism	• Asymmetrical resting tremor, as a 'pill-rolling' action of the hands, may affect chin, lips, legs, and trunk, increased by stress or emotions • Bradykinesia, Rigidity, Flexed posture, • Short, shuffling steps • Micrographia, Mask-like face • Depression & dementia are common • May be history of anti-psychotic use
Essential tremor	• Postural tremor: worse if arms outstretched • Improved by alcohol and rest • Titubation • Often strong family history • Can affect the person's ability to perform activities of daily living
Anxiety	History of depression
Thyrotoxicosis	Usual thyroid signs e.g. Weight loss, tachycardia, feeling hot...
Hepatic encephalopathy	History of chronic liver disease
Carbon dioxide retention	History of COPD
Cerebellar disease	• Intention tremor occurring at the end of a purposeful movement such as touching a finger to the tip of the person's nose. • This tremor may be accompanied by dysarthria, nystagmus, gait problems, and postural tremor of the trunk and neck.

Holmes' tremor or rubral tremor:

- It is secondary to a lesion in the **red nucleus** and can occur following a stroke in this area.
- It classically produces an irregular low frequency tremor which is a combination of a rest, postural and action tremor.
- It is described as a 'wing-beating' type of tremor and is most prominent when the affected person is active or is maintaining a particular posture. Signs of ataxia and weakness can occur.

Physiological tremor:

- A postural tremor occurring in every normal individual.
- It is rarely visible to the eye and may be heightened by strong emotion (such as anxiety or fear), physical exhaustion, hypoglycaemia, hyperthyroidism, heavy metal poisoning, stimulants, alcohol withdrawal, caffeine, or fever.

Essential tremor

- Previously called benign essential tremor
- Autosomal dominant condition, often strong family history.
- usually affects both upper limbs

Features:

- 1) postural tremor: worse if arms outstretched
- 2) improved by alcohol and rest
- 3) most common cause of titubation (head tremor)

Management:

- 1) **propranolol** is first-line
- 2) **primidone** is sometimes used (also 1st line)

Causes of Parkinsonism

- 1) Parkinson's disease
- 2) progressive supranuclear palsy
- 3) multiple system atrophy
- 4) Wilson's disease
- 5) post-encephalitis Parkinson (oculogyric crisis)
- 6) dementia pugilistica (secondary to chronic head trauma e.g. boxing)
- 7) antipsychotics, metoclopramide - see below
- 8) carbon monoxide CO, MPTP

Drugs causing Parkinsonism:

- 1) phenothiazines: e.g. chlorpromazine, prochlorperazine
- 2) butyrophenones: haloperidol, droperidol
- 3) metoclopramide

Domperidone does not cross the blood-brain barrier and therefore does not cause extra-pyramidal side-effects

- MPTP (methyl-phenyl-tetrahydropyridine) is a neurotoxin precursor to MPP⁺, which causes permanent symptoms of Parkinson's disease by destroying dopaminergic neurons in the substantia nigra.
- While MPTP itself has no psychoactive effects, the compound may be accidentally produced during the manufacture of MPPP.
- MPTP itself is not toxic, and as a lipophilic compound can cross BBB. Once inside the brain, MPTP is metabolized into the toxic cation 1-methyl-4-phenylpyridinium (MPP⁺) by the enzyme MAO-B of glial cells. MPP⁺ kills primarily dopamine-producing neurons in the substantia nigra.
- Because MPTP itself is not directly harmful, toxic effects of acute MPTP poisoning can be mitigated by the administration of (MAOIs) such as selegiline-----> prevent the metabolism of MPTP to MPP⁺ by inhibiting the action of MAO-B, minimizing toxicity and preventing neural death.

NB: 1-methyl-4-phenyl-4-propionoxypiperidine (MPPP) is an opioid analgesic analog of pethidine (meperidine) . Chemically, it is a reversed ester of pethidine which has about 70% of the potency of morphine.

Parkinson's disease

- a progressive neurodegenerative condition
- Caused by **degeneration of dopaminergic neurons** in the **substantia nigra**.
- This results in a classic triad of features: **bradykinesia**, **tremor** and **rigidity**
- The symptoms of Parkinson's disease are characteristically **asymmetrical**.

Epidemiology:

- around twice as common in men
- mean age of diagnosis is 65 years

Features:

Bradykinesia:

- poverty of movement also seen, sometimes referred to as hypokinesia
- short, shuffling steps with reduced arm swinging
- difficulty in initiating movement

Tremor:

- most marked at rest, 3-5 Hz
- worse when stressed or tired
- typically 'pill-rolling', i.e. in the thumb and index finger
- It affects the most distal part of the limb and at onset typically appears in only a single arm or leg, becoming bilateral later

Rigidity:

- lead pipe
- cogwheel: due to superimposed tremor

Other characteristic features:

- 1) mask-like facies
- 2) drooling of saliva
- 3) impaired olfaction
- 4) flexed posture
- 5) micrographia
- 6) psychiatric features:
 - ✓ Depression is the most common feature (affects about 40%);
 - ✓ dementia,
 - ✓ psychosis and
 - ✓ sleep disturbances may also occur
- 7) REM sleep behaviour disorder

Drug-induced Parkinsonism has slightly different features to Parkinson's disease:

- motor symptoms are generally rapid onset and bilateral
- Rigidity and rest tremor are **uncommon** ????

Parkinson's disease management

- Currently accepted practice in the management of patients with Parkinson's disease (PD) is to delay treatment until onset of disabling symptoms & then to introduce a dopamine receptor agonist.
- If the patient is elderly, levodopa is sometimes used as an initial treatment.

Dopamine receptor agonists:

- ☒ Bromocriptine, cabergoline,
- ☒ ropinirole
- ☒ apomorphine: one of the older dopamine receptor agonists

Ergot-derived dopamine receptor agonists:

- ☒ Bromocriptine, cabergoline, pergolide
- ☒ Have been associated with **pulmonary, retroperitoneal and cardiac fibrosis**.
- ☒ The Committee on Safety of Medicines advice that an echocardiogram, ESR, creatinine and chest x-ray should be obtained prior to treatment and patients should be closely monitored
- ☒ pergolide was withdrawn from the US market in March 2007 due to concern regarding increased incidence of **valvular dysfunction**
- patients should be warned about the potential for dopamine receptor agonists to cause:
 - ✓ **impulse control disorders** and
 - ✓ **excessive daytime somnolence**
- More likely than levodopa to cause **hallucinations** in older patients.
- **Nasal congestion** and **postural hypotension** are also seen in some patients

People with an impulse control disorder can't resist the urge to do something harmful to themselves or others. include addictions to alcohol, drugs, eating disorders, compulsive gambling, paraphilias sexual fantasies and behaviors involving non-human objects, suffering, humiliation or children, compulsive hair pulling, stealing, fire setting and intermittent explosive attacks of rage.

Levodopa:

- usually combined with a decarboxylase inhibitor (e.g. carbidopa or benserazide) to prevent peripheral metabolism of L-dopa to dopamine
- reduced effectiveness with time (usually by 2 years)
- **no use in neuroleptic induced parkinsonism**

Adverse effects:

- 1) dyskinesia (involuntary writhing movements)
- 2) 'on-off' effect
- 3) Drowsiness, postural hypotension
- 4) cardiac arrhythmias, palpitations
- 5) anorexia, nausea, vomiting & dry mouth
- 6) psychosis
- 7) reddish discolouration of urine upon standing

Monoamine Oxidase-B (MAO-B) inhibitors

- e.g. **Selegiline**
- inhibits the breakdown of dopamine secreted by the dopaminergic neurons

Catechol-O-Methyl Transferase (COMT) inhibitors:

- e.g. **Entacapone, tolcapone**
- COMT is an enzyme involved in the breakdown of dopamine.
- used in conjunction with levodopa in patients with established PD

Amantadine:

- mechanism is not fully understood, probably increases dopamine release and inhibits its uptake at dopaminergic synapses

Side-effects include:

- 1) ataxia,
- 2) slurred speech,
- 3) confusion,
- 4) dizziness and
- 5) livedo reticularis

Antimuscarinics:

- block cholinergic receptors
- now used more to treat **drug-induced parkinsonism** rather than idiopathic Parkinson's disease
- help tremor and rigidity
- e.g.
 - ☒ procyclidine,
 - ☒ benzotropine,
 - ☒ trihexyphenidyl (benzhexol)

SOME COMMENTS FROM ON EXAMINATION

- Rasagiline is an irreversible inhibitor of monoamine oxidase and can be used as a monotherapy in early Parkinson's disease or as an adjunct therapy in more advanced cases.
- Amantadine may be used as a treatment for early Parkinson's disease but should not be the drug of first choice.
- Apomorphine is a dopamine agonist used subcutaneously later in the disease process in people with severe motor complications unresponsive to oral medication.
- Entacapone is a catechol-O-methyl transferase inhibitor which may be used to reduce motor fluctuations in later Parkinson's disease.
- Trihexyphenidyl is an anticholinergic which can be used as a symptomatic treatment in young patients with early Parkinson's disease and severe tremor but should not be the drug of first choice due to limited efficacy and the propensity to cause neuropsychiatric side effects.

Neuroleptic Malignant Syndrome

- a rare but dangerous condition seen in patients taking antipsychotic medication
- Caused by a sudden reduction in dopamine activity, either from blockade of dopamine receptors or withdrawal of dopaminergic agents.
- It carries a mortality of up to 10% and can also occur with atypical antipsychotics.
- It may also occur with dopaminergic drugs (such as levodopa) for Parkinson's disease, usually when the drug is suddenly stopped or the dose reduced.

Features:

- ☒ more common in young male patients
- ☒ Onset usually in first 10 days of treatment or after increasing dose but it can occur at any time during the treatment with antipsychotic medications.
- ☒ Concomitant treatment with lithium or anticholinergics may increase the risk of NMS.
 - 1) **Fever**
 - 2) **rigidity**
 - 3) **Altered mental status**
 - 4) **Autonomic dysfunction**
 - 5) tachycardia
 - 6) raised creatine kinase:
 - ☒ present in most cases
 - ☒ always elevated ($>1000 \text{ IU/L}^{-1}$)
 - ☒ reflecting myonecrosis secondary to intense muscle contracture
 - 7) leukocytosis may also be seen

Management:

- 1) stop antipsychotic
 - 2) IV fluids to prevent renal failure
 - 3) Reduction of body temperature with antipyretics.
 - 4) **dantrolene*** may be useful in selected cases
 - 5) **bromocriptine, dopamine agonist**, may also be used
- *thought to work by decreasing excitation-contraction coupling in skeletal muscle by binding to the ryanodine receptor, and decreasing the release of calcium from the sarcoplasmic reticulum

NB: NMS is most often caused by antipsychotic drugs (e.g. olanzapine, risperidone, aripiprazole, amisulpride, quetiapine, chlorpromazine, haloperidol and clozapine). However a wide range of drugs can also cause NMS. These include dopaminergic medication i.e. levodopa and this often occurs when these medications are stopped abruptly, anti-dopaminergic medication such as metoclopramide and even drugs without anti-dopaminergic effects such as lithium can also cause NMS.

Malignant hyperthermia

- A condition often seen following administration of **anaesthetic agents**
- characterised by **hyperpyrexia** and **muscle rigidity**
- cause by **excessive release of Ca²⁺** from the **sarcoplasmic reticulum** of skeletal muscle
- associated with defects in a gene on **chromosome 19** encoding the **ryanodine receptor**, which controls Ca²⁺ release from the sarcoplasmic reticulum
- neuroleptic malignant syndrome may have a similar aetiology

Causative agents:

- 1) halothane
- 2) suxamethonium
- 3) other drugs: antipsychotics (neuroleptic malignant syndrome)

Investigations:

- 1) CK raised
- 2) contracture tests with halothane and caffeine

Management

- **dantrolene**: prevents Ca²⁺ release from the sarcoplasmic reticulum
-

Multiple system atrophy

Shy-Drager syndrome is a type of multiple system atrophy

Features:

- 1) parkinsonism
 - 2) autonomic disturbance:
 - ✓ atonic bladder, disturbance of sphincter control, anhidrosis, , impotence
 - ✓ postural hypotension,
 - 3) cerebellar signs
-

Progressive supranuclear palsy

- aka Steele-Richardson-Olszewski syndrome
- a 'Parkinson Plus' syndrome

Features:

- 1) **impairment of vertical gaze**:
 - ✓ down gaze worse than up gaze
 - ✓ patients may complain of difficulty reading or descending stairs)
- 2) **parkinsonism**
- 3) falls
- 4) slurring of speech
- 5) **cognitive impairment**

Management: poor response to L-dopa

Parkinsonism+ impairment of vertical gaze

Chorea

- Caused by damage to the BG, especially the caudate nucleus.
- Involuntary, rapid, jerky movements which often move from one part of the body to another.
- Slower, sinuous بطيئة ومتعرجة movement of the limbs is termed **athetosis**.

Causes of chorea:

- 1) Huntington's disease, Wilson's disease, ataxic telangiectasia
- 2) SLE, anti-phospholipid syndrome
- 3) rheumatic fever: Sydenham's chorea
- 4) pregnancy: chorea gravidarum
- 5) neuroacanthocytosis
- 6) thyrotoxicosis
- 7) polycythaemia rubra vera PRV
- 8) CVD
- 9) Drugs:
 - ✓ oral contraceptive pill,
 - ✓ L-dopa,
 - ✓ antipsychotics
- 10) CO carbon monoxide poisoning (also can cause parkinsonism)

Huntington's disease

- An autosomally inherited condition
- Due to an expanded **CAG trinucleotide** repeat on the short arm of **chromosome 4**.
- It is characterised by **progressive dementia** and worsening **choreiform movements**.
- Symptoms typically appear between **30- 50 years** of age.
- Genetic testing now provides an accurate method of establishing the diagnosis.
- Average life span after clinical onset is about 15 years.

Sydenham's chorea:

- Patient presents with acute chorea as a result of **streptococcal throat infection**
- This tends to occur in children presenting initially with irritability and inattentiveness.
- This then progresses to generalised chorea with **speech involvement** occurring in 20% of cases.
- Those who have had several attacks in childhood may develop chorea in adulthood when exposed to drugs such as the oral contraceptive pill, phenytoin or digoxin, or during pregnancy.
- Treatment is for chorea with **tetrabenazine** or **sulpiride** and a **course of penicillin** for acute infection.

Hemiballism

- The presence of severe sudden, jerking flinging movements affecting **proximal muscles** and following no particular pattern is typical for hemiballism.
- The site of the lesion is in the **contralateral subthalamic nucleus**, infarction being the commonest cause (also neoplasia or hyperglycemia).
- Bilateral ballismus is rare and implicates a metabolic cause, usually non-ketotic hyperosmolar coma (HONK).
- Symptoms may decrease whilst the patient is asleep.

Management:

- ☒ Treatment of the cause
- ☒ Usually the flinging movements stop spontaneously in the next four to eight weeks
- ☒ **Tetrabenazine** is **the treatment of choice**.
(Dramatic response but recurrent symptoms on lowering dose)
- Antidopaminergic agents (e.g. Haloperidol) ???

Cerebrospinal fluid:

Normal values of cerebrospinal fluid (CSF) are as follows:

- pressure = 60-150 mm (patient recumbent)
- protein = 0.2-0.4 g/l
- glucose = $> 2/3$ blood glucose
- cells: red cells = 0, white cells $< 5/\text{mm}^3$

Raised lymphocytes:

- 1) viral meningitis/encephalitis
- 2) TB meningitis
- 3) partially treated bacterial meningitis
- 4) Lyme disease
- 5) Behcet's, SLE
- 6) lymphoma, leukaemia

Raised protein:

- 1) Guillain-Barre syndrome
- 2) tuberculous, fungal and bacterial meningitis
- 3) viral encephalitis
- 4) spinal block (Froin's syndrome*)

*describes an increase in CSF protein below a spinal canal blockage (e.g. tumor, disc, infection)

Meningitis

CSF analysis

	Bacterial	Viral	Tuberculous
Appearance	Cloudy	Clear/cloudy	Slight cloudy, fibrin web
Glucose	Low (< 1/2 plasma)	60-80% of plasma glucose*	Low (< 1/2 plasma)
Protein	High (> 1 g/l)	Normal/raised	High (> 1 g/l)
White cells	10 - 5,000 polymorphs/mm ³	15 - 1,000 lymphocytes/mm ³	10 - 1,000 lymphocytes/mm ³

Mumps is associated with a low glucose level in a proportion of cases.
A low glucose may also be seen in herpes encephalitis

Tuberculous meningitis

- The Ziehl-Neelsen stain is only 20% sensitive in the detection of tuberculous meningitis and therefore
- PCR is sometimes used (sensitivity = 75%)

Causes for aseptic meningitis:

- Behçet's syndrome, Systemic diseases.
 - viruses - commonly **enteroviruses**, e.g. polio, **coxsackievirus**, **echovirus**
 - partially treated bacterial meningitis
 - fungal meningitis
 - parasites
 - drugs, e.g. intravenous immunoglobulin, and some intrathecal medications
-
- ☒ *Listeria* meningitis should always be considered in patients with meningitis associated with **brain stem involvement**, and in **immunosuppressed patients**.
 - ☒ The treatment of choice is gentamicin and ampicillin.
 - ☒ Neutrophils usually predominate in the cerebrospinal fluid (CSF) in patients with bacterial meningitis. However, a lymphocytosis is seen in approximately 10% of patients.
 - ☒ Lymphocytes may predominate in 30% of patients with meningitis caused by Gram negative bacilli, or in *Listeria monocytogenes* infection.
 - ☒ Note that this means that 70% of patients with *Listeria* meningitis will have a neutrophilic CSF.
 - ☒ A lymphocytic CSF predominates in TB and fungal meningitis.

Herpes simplex encephalitis

- a common topic in the exam
- The virus characteristically affects the **temporal lobes** - questions may give the result of imaging or describe temporal lobe signs e.g. **aphasia**.

Features:

- 1) fever, headache, psychiatric symptoms, seizures, vomiting
- 2) focal features e.g. aphasia
- 3) peripheral lesions (e.g. cold sores) **have no relation** to presence of HSV encephalitis

Pathophysiology:

- **HSV-1** responsible for **95%** of cases in adults
- typically affects **temporal** and **inferior frontal** lobes

Investigation:

- 1) CSF: **lymphocytosis, elevated protein**
- 2) PCR for HSV: **diagnostic in 95%**
- 3) CT:
 - ☒ Medial temporal and inferior frontal changes (e.g. **petechial haemorrhages**)
 - ☒ normal in one-third of patients
- 4) **MRI is better** than CT
- 5) EEG pattern: **lateralised periodic discharges at 2 Hz**

Treatment

- **intravenous acyclovir**

Prognosis:

- The prognosis is dependent on whether acyclovir is commenced early.
- If treatment is started promptly the mortality is 10-20%.
- Left untreated the mortality approaches 80%

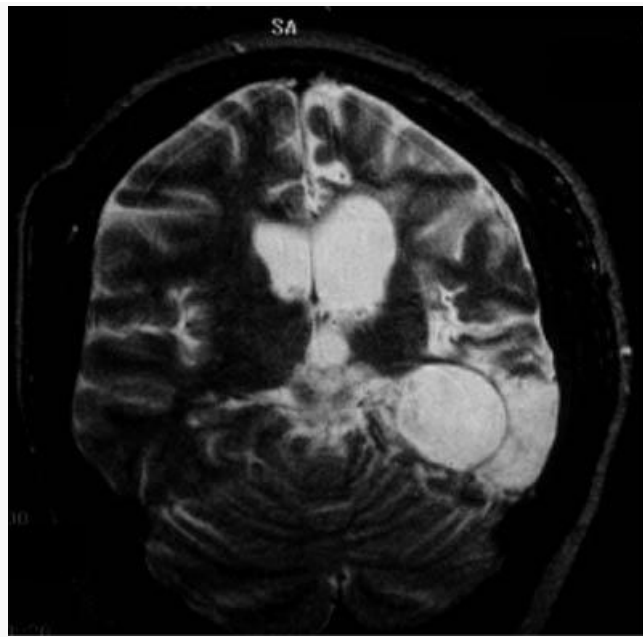
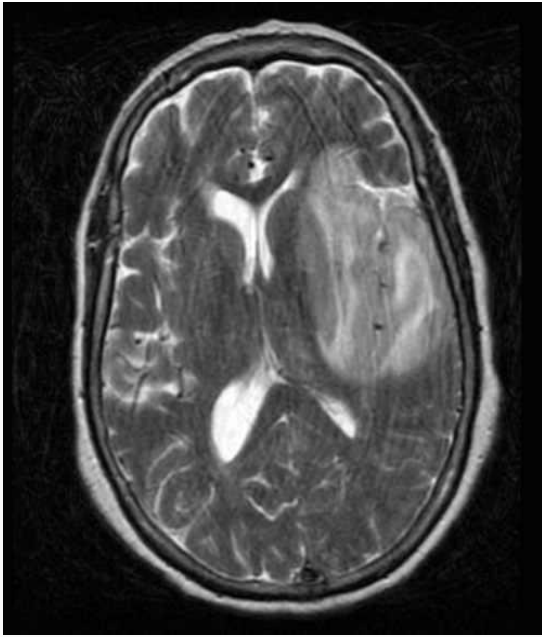


Image 1 MRI of a patient with HSV encephalitis. There is **hyperintensity** of the affected white matter and cortex in the medial temporal lobes and insular cortex.

Image 2 The MRI demonstrates a temporoparietal dense lesion.

The diagnosis is reliably confirmed by the presence of herpes simplex virus in the cerebrospinal fluid by polymerase chain reaction.

HIV Neurocomplications

Focal neurological lesions

Toxoplasmosis

- Toxoplasma encephalitis is the commonest cause of focal brain disease in HIV/AIDS, occurring at CD4 counts of less than 100 cells/mm³
- accounts for around 50% of cerebral lesions in patients with HIV
- Although *Toxoplasma gondii* may also cause a retinitis in association with HIV/AIDS, it need not occur concomitantly with central nervous system disease.
- constitutional symptoms, headache, confusion, drowsiness

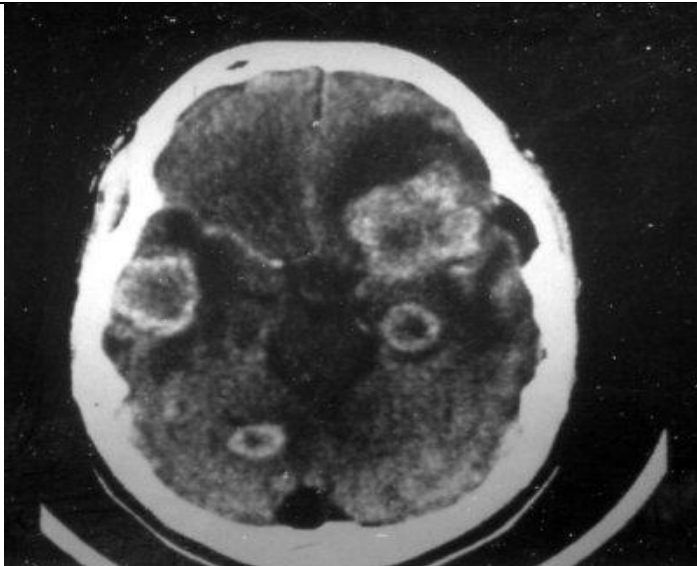
CT:

- 1) usually **single** or **multiple ring enhancing lesions**,
- 2) mass effect may be seen

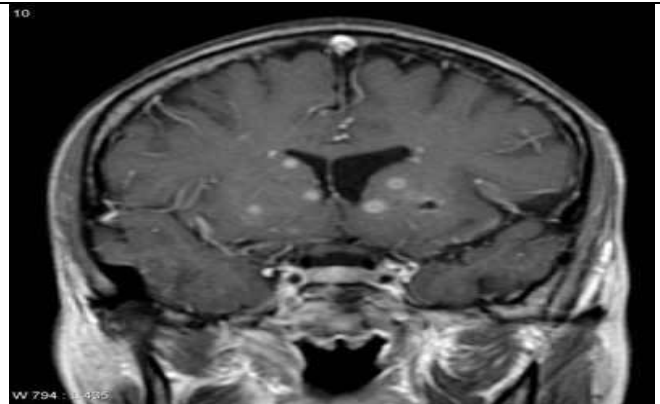
Management:

- 1) **sulfadiazine** and
- 2) **pyrimethamine**

☒ Patients must subsequently be maintained on long term suppressive therapy to prevent relapse.



Cerebral toxoplasmosis: CT scan with contrast showing multiple ring enhancing lesions



Cerebral toxoplasmosis: MRI (T1 C+) demonstrates multiple small peripherally enhancing nodules located predominantly in the basal ganglia as well as the central portions of the cerebellar hemispheres. Only a small amount of surrounding oedema is present.

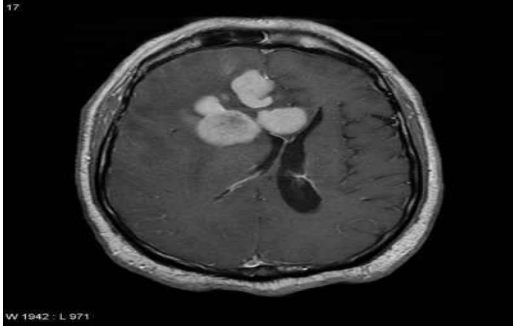
Primary CNS lymphoma

- accounts for around 30% of cerebral lesions
- associated with the **Epstein-Barr virus**

CT: single or multiple **homogenous enhancing lesions**

Treatment:

- 1) Generally involves **steroids** (may significantly reduce tumour size),
- 2) Chemotherapy (e.g. **methotrexate**) + with or without whole **brain irradiation**.
- 3) Surgical may be considered for lower grade tumours



Primary CNS lymphoma: MRI (T1 C+) demonstrates a large multilobulated mass in the right frontal lobe. It homogeneously enhances and extends to involve the caudate and the periventricular area. There is significant mass effect.



Primary CNS lymphoma: Non-contrast CT demonstrates a hyper-attenuating mass adjacent to the left lateral ventricle, with no calcification or hemorrhage.

Differentiating between toxoplasmosis and lymphoma

Toxoplasmosis	Lymphoma SSS
• Multiple lesions • Ring or nodular enhancement • Thallium SPECT negative	• Single lesion • Solid (homogenous) enhancement • Thallium SPECT positive

Tuberculosis

- much less common than toxoplasmosis or primary CNS lymphoma
- CT: single enhancing lesion

Generalised HIV neurocomplications

Encephalitis

- may be due to CMV or HIV itself
- HSV encephalitis but is relatively rare in the context of HIV
- CT: oedematous brain

Cryptococcus neoformans

- Most common fungal infection of CNS, CD4 < 50 cells/mm³ and
- May be associated with a **pneumonitis**.
- *Cryptococcus* can cause **papular skin lesions** that **resemble molluscum contagiosum**.
- The disease is commoner in **African populations**.

Features:

Meningitis is typical presentation but may occasionally cause a **space occupying lesion**

- 1) headache, fever, malaise,
- 2) nausea/vomiting,
- 3) seizures, focal neurological deficit

☒ CSF:

- high opening pressure,
- **India ink test positive thick polysaccharide capsule** around the cell

☒ CT:

- **meningeal enhancement**,
- cerebral oedema

Treatment:

- 1) **Amphotericin B** and **flucytosine (5FC)**;
- 2) Patients then require lifetime suppression with **fluconazole**.



India ink stain shows: the thick polysaccharide capsule is highlighted around the cell (shown in slide).

Progressive multifocal leukoencephalopathy (PML)

- Widespread demyelination
- due to infection of oligodendrocytes by JC virus (a polyoma DNA virus)
- **symptoms:**
Subacute onset of:
 - behavioral changes,
 - speech, motor, visual impairment
- **CT:**
 - ✓ Single or multiple lesions,
 - ✓ no mass effect,
 - ✓ Don't usually enhance.
- **MRI:**
 - ✓ Better
 - ✓ high-signal demyelinating white matter lesions are seen
- A brain biopsy would be the definitive diagnostic test showing:
 - ⇒ Asymmetric foci of demyelination and
 - ⇒ Intranuclear inclusions containing the JC virus.

AIDS dementia complex

- Caused by HIV virus itself
- Symptoms:
 - ✓ behavioral changes,
 - ✓ motor impairment
- CT: cortical and subcortical atrophy

Neurocutaneous syndromes

Neurofibromatosis

- There are two types of neurofibromatosis, NF1 and NF2.
- Both are inherited in an **autosomal dominant** fashion

1) NF1:

- ☒ is also known as **von Recklinghausen's syndrome**
- ☒ It is caused by a gene mutation on chromosome 17 which encodes neurofibromin
- ☒ affects around 1 in 4,000

2) NF2:

- ☒ caused by gene mutation on chromosome 22
- ☒ affects around 1 in 100,000
- ☒ **Haemangiomas** of the CNS (usually retina or cerebellum) ???

NF1 von Recklinghausen's syndrome	NF2
• Café-au-lait spots (≥ 6, 15 mm in diameter) • Axillary/groin freckles النمش • Peripheral neurofibromas • Iris: Lisch nodules in $> 90\%$ • Scoliosis • Pheochromocytomas	Bilateral acoustic neuromas

Mnemonic: NF1: Has 17 letters so, a gene mutation on chromosome 17 NF2: gene mutation on chromosome 22

Tuberous sclerosis

- A genetic condition of **autosomal dominant** inheritance.
- Like neurofibromatosis, the majority of features seen in TS are neuro-cutaneous

Cutaneous features:

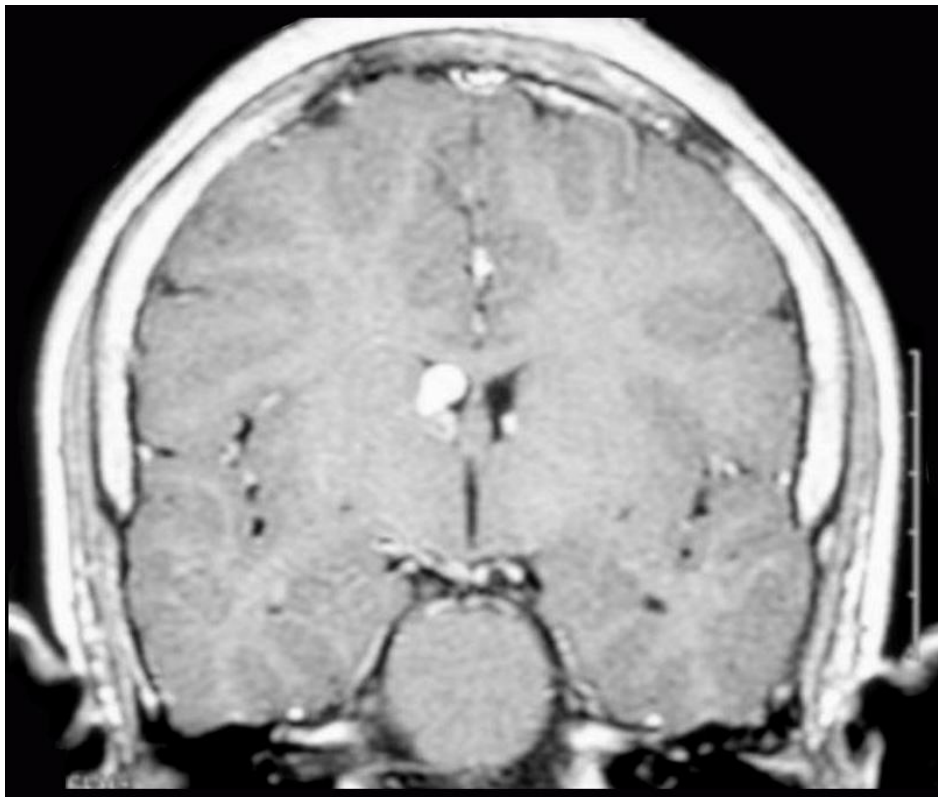
- 1) **depigmented 'ash-leaf' spots** which fluoresce under UV light
- 2) **Shagreen patches: roughened patches** of skin over **lumbar spine**
- 3) **adenoma sebaceum**: butterfly distribution over nose
- 4) **subungual fibromata**: fibromata beneath nails
- 5) **café-au-lait spots** may be seen

These of course are more commonly associated with neurofibromatosis.

However a 1998 study of 106 children with TS found café-au-lait spots in 28% of patients

Neurological features:

- 1) developmental delay
- 2) **intellectual impairment**
- 3) epilepsy (infantile spasms or partial)
- 4) **retinal hamartomas**: dense white areas on retina (**phakomata**)
- 5) gliomatous changes can occur in the brain lesions
- 6) **rhabdomyomas** of the heart
- 7) polycystic kidneys, renal angiomyolipomata



This patient has tuberous sclerosis. Fibromas may also develop within the central nervous system, where they calcify typically in the periventricular area.

Von Hippel-Lindau syndrome (VHL)

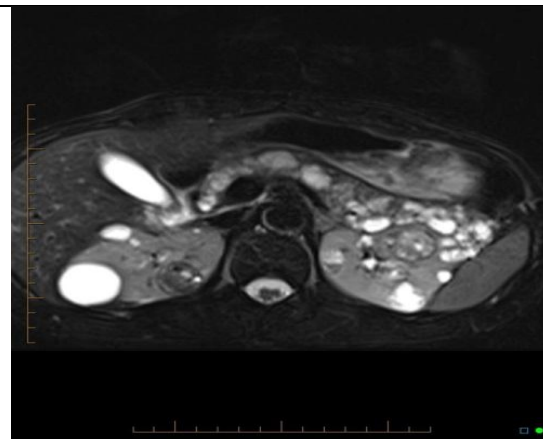
- Autosomal dominant condition predisposing to neoplasia.
- It is due to an abnormality in the VHL gene located on short arm of chromosome 3

Features: cerebellar & retinal haemangiomas plus Renal, extrarenal, suprarenal,

- 1) cerebellar haemangiomas
- 2) retinal haemangiomas: vitreous hemorrhage
- 3) Retinal haemangiomas are bilateral in 25% of patients
- 4) renal cysts (premalignant), renal cell carcinoma
- 5) extra-renal cysts: epididymal, pancreatic, hepatic
- 6) Suprarenal: pheochromocytoma
- 7) endolymphatic sac tumors



CT scan showing a cerebellar haemangioma in a patient with Von Hippel-Lindau syndrome.



MRI showing renal cysts in patient with known Von Hippel-Lindau syndrome.

Fabry disease

- an X linked lysosomal storage disease
- caused by mutations in the alpha-galactosidase A gene, which
- leads to accumulation of lysosomes in vascular endothelial cells and smooth muscle cells affecting the brain, myocardium and the dorsal root ganglion

Patients can present with:

- 1) Small vessel stroke
- 2) Painful peripheral neuropathy
- 3) Renal disease
- 4) Skin stigmata,(multiple skin angiokeratomas) and
- 5) Myocardial infarction.

Diagnosis is clinical, although β -galactosidase activity can be measured and there is a genetic test available, which is helpful particularly in females who may have normal or low normal levels of activity.

Internuclear ophthalmoplegia

- a cause of **horizontal disconjugate** eye movement
- due to a lesion in the **medial longitudinal fasciculus (MLF)**, which connects the **IIIrd**, **IVth** and **VIth** cranial nuclei

Features:

- 1) **impaired adduction** of the eye on the same side as the lesion
- 2) horizontal nystagmus of **the abducting eye** on the contralateral side

Causes:

- 1) multiple sclerosis **MS**
- 2) **vascular** disease

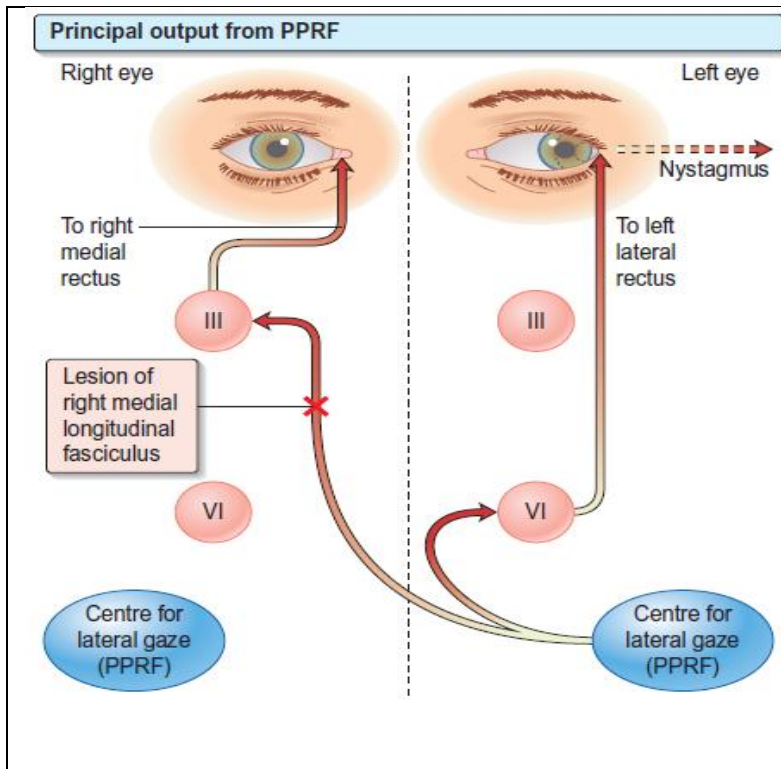


Figure 22.6 PPRF and INO.

Impulses from PPRF pass via ipsilateral VI th nerve nucleus to lateral rectus muscle (ABduction) and via medial longitudinal fasciculus to opposite III rd nerve nucleus and thus to opposite medial rectus muscle (ADduction).

A lesion of the MLF (X) causes:

- 1) Failure of or slow ADduction in the right eye and
- 2) nystagmus in the left eye with left lateral gaze.

PPRF, para-median pontine reticular formation

INO: internuclear ophthalmoplegia

MLF: medial longitudinal fasciculus.

Progressive supranuclear palsy

- aka Steele-Richardson-Olszewski syndrome
- a 'Parkinson Plus' syndrome

Features:

- 1) impairment of vertical gaze:
 - ✓ down gaze worse than up gaze
 - ✓ patients may complain of difficulty reading or descending stairs)
- 2) parkinsonism
- 3) falls
- 4) slurring of speech
- 5) cognitive impairment

Management: poor response to L-dopa

Parkinsonism, impairment of vertical gaze

Nystagmus

Upbeat nystagmus up الى فوق يعمل.

- cerebellar vermis lesions

Downbeat nystagmus: indicates a craniomedullary junction pathology down والى تحت يعمل

- Arnold-Chiari malformation

Pupillary light reflex

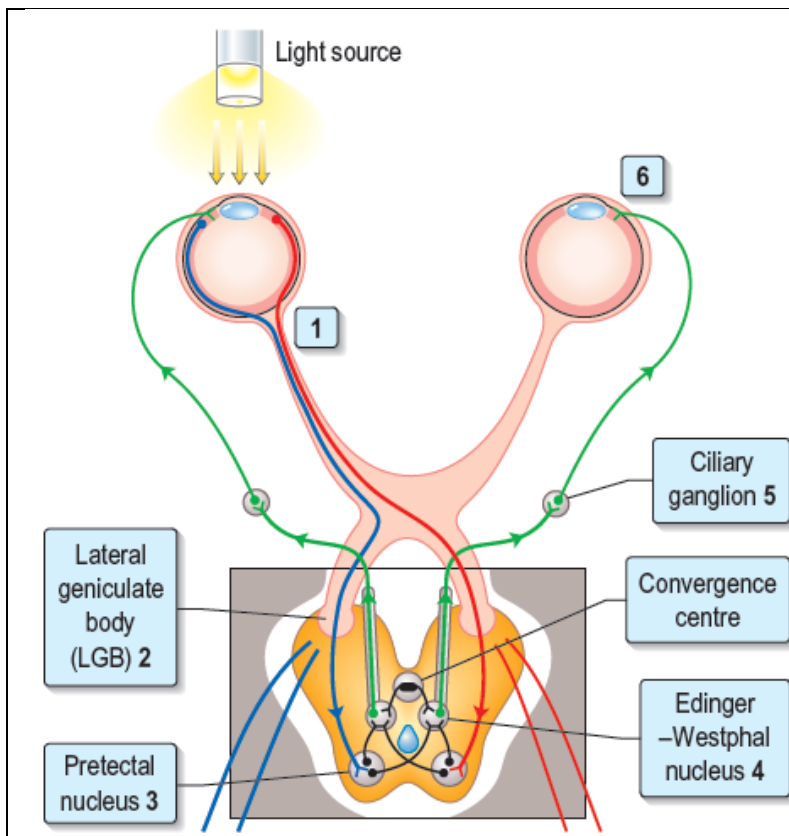


Figure 22.5
Pupillary light reflex.

Afferent pathway:

- 1) Light activates optic nerve axons.
- 2) Axons (some decussating at the chiasm) pass through each lateral geniculate body, and
- 3) Synapse at pretectal nuclei.

Efferent pathway:

- 4) Action potentials pass to Edinger-Westphal nuclei of III rd nerve, then,
- 5) Via **parasympathetic neurones** in III rd nerves to cause (6) **Miosis**.

Bilateral لاحظ ان كله على الناحيتين

Horner's syndrome

- The sympathetic nervous supply to the eye is a 3 neurons pathway originating in **hypothalamus** and descending by way of the **brainstem** and **cervical cord** to **T1 nerve root**, **paravertebral sympathetic chain** and, on via the **carotid artery** wall, to the eye.
- Damage to any part of the pathway results in Horner's syndrome.
- This is significant not only because it affects vision but also because it may indicate a serious underlying pathology.

Causes Of Horner's syndrome:

Hypothalamic, hemisphere and brainstem lesions (central)

- Massive cerebral infarction
- Brainstem demyelination or lateral medullary infarction

Cervical cord (central)

- Syringomyelia and cord tumours

T1 root (pre)

- Apical lung tumour or TB
- Cervical rib
- Brachial plexus trauma

Sympathetic chain and carotid artery in neck (post)

- Following thyroid/laryngeal/carotid surgery
- Carotid artery dissection
- Neoplastic infiltration
- Cervical sympathectomy

Miscellaneous

- Congenital
- Cluster headache, usually transient
- Idiopathic

Features:

- 1) **ptosis**
- 2) **miosis** (small pupil)
- 3) **anhidrosis** (loss of sweating one side)
- 4) **enophthalmos**

*in reality the appearance is due to a narrow palpebral aperture rather than true enophthalmos

Distinguishing between causes:

- 1) **heterochromia** (difference in iris colour) is seen in congenital Horner's
- 2) **anhidrosis**: see below

Central lesions	Pre-ganglionic lesions	Post-ganglionic lesions
Anhidrosis of the face, arm and trunk	Anhidrosis of the face	No anhidrosis
Stroke Syringomyelia Multiple sclerosis Tumour Encephalitis	Pancoast's tumour Cervical rib Thyroidectomy Trauma	Carotid artery dissection Carotid aneurysm Cavernous sinus thrombosis Cluster headache

Holmes-Adie pupil (Myotonic pupil)



- 1) It is a benign condition most commonly seen in **young women**
- 2) it is common and usually **unilateral** (80% of cases)
- 3) May occur after an episode of **zoster infection**.
- 4) This is a **dilated**, often **irregular** pupil;
- 5) once the pupil has constricted it remains small for an abnormally long time
- 6) **Slowly reactive** to **accommodation** but **very poorly** (if at all) to light.
- 7) This is due to denervation in the **ciliary ganglion** (parasympathetic), of unknown cause, and has no other pathological significance.
- 8) At the beginning of the condition the pupil is large, but over time becomes small and poorly reactive.
- 9) In adults it tends to be a benign condition and is simply observed, however infants are usually referred because of an association with familial dystonias

Diagnosis:

- 1) Slit lamp examination may reveal small worm like contractions of the iris
- 2) **pilocarpine eye drops**:
 - ✓ The usual diagnostic test
 - ✓ Weak pilocarpine eye drops induce vigorous pupil contraction on the affected side (cholinergic denervation supersensitivity), but only weak contraction of the pupil on the unaffected side with this dilute dose of pilocarpine.

Holmes-Adie syndrome

- association of Holmes-Adie pupil + absent ankle/knee reflexes

Argyll Robertson pupil

(Accommodate but not react; prostitute pupil) **لامؤاخذة**

- One of the classic pupillary syndromes. (Now rarely seen in clinical practice)
- It is sometimes seen in neurosyphilis and is often said to be the prostitute's pupil - **accommodates but doesn't react**
- Another mnemonic used for the Argyll-Robertson Pupil (ARP) is Accommodation Reflex Present (ARP) but Pupillary Reflex Absent (PRA) **ARP----- PRA**

Features:

- 1) A small, irregular pupil
- 2) no response to light but there is a response to accommodate

Causes:

- 1) syphilis (Once Considered diagnostic of neurosyphilis)
- 2) diabetes mellitus (It is now only occasionally seen in diabetes or MS)
- 3) The lesion is in the brainstem surrounding the aqueduct of Sylvius.

Mydriasis

Causes of mydriasis (large pupil):

- 1) congenital
- 2) third nerve III palsy
- 3) traumatic iridoplegia
- 4) Holmes-Adie pupil
- 5) phaeochromocytoma

Drug causes of mydriasis

- 1) topical mydriatics: tropicamide, atropine
- 2) sympathomimetic drugs: amphetamines, cocaine.....مهم جدا
- 3) anticholinergic drugs: TCAs

Miosis

Causes of miosis (small pupil)

- 1) congenital
- 2) senile miosis
- 3) Horner's syndrome
- 4) Argyll-Robertson pupil
- 5) pontine hemorrhage

Drugs causes:

- 1) opiates (morphin)
- 2) organophosphate toxicity
- 3) parasympathomimetics: pilocarpine

Ptosis

Ptosis may be unilateral or bilateral

Causes of bilateral ptosis:

- 1) myotonic dystrophy
- 2) myasthenia gravis*
- 3) syphilis
- 4) congenital

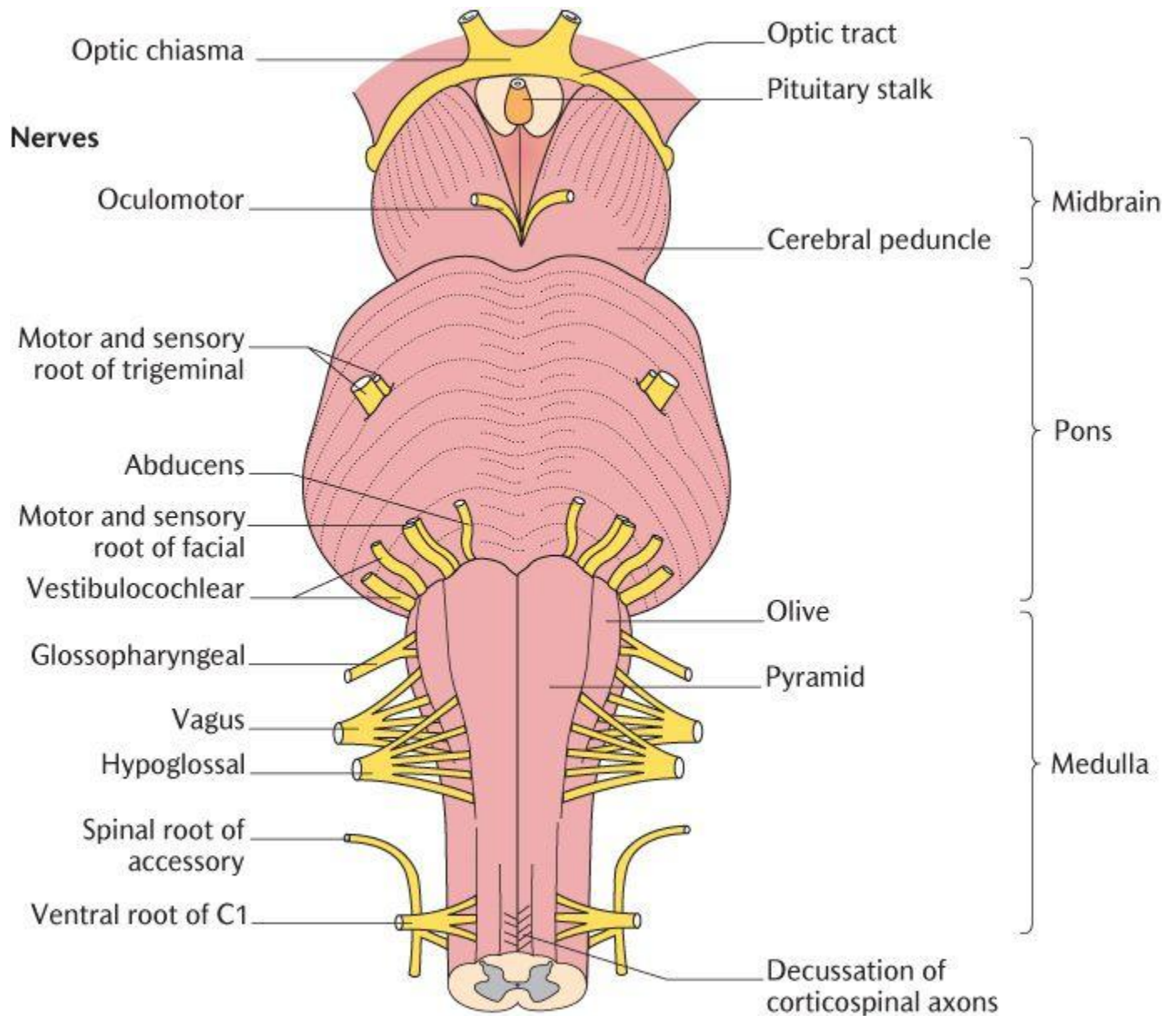
Causes of unilateral ptosis: as above plus:

- 1) third nerve palsy
- 2) Horner's

Cranial Nerves

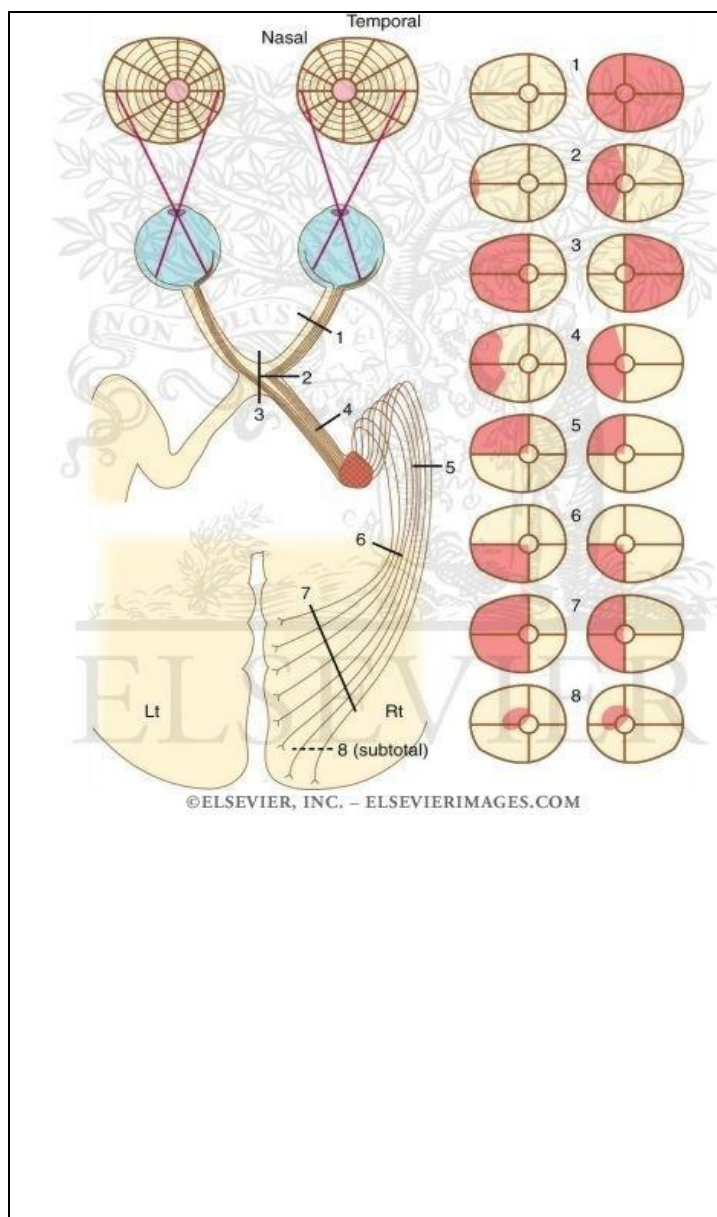
Table 22.3 Cranial nerves

Number	Name	Main clinical action
I	Olfactory	Smell
II	Optic	Vision, fields, afferent light reflex
III	Oculomotor	Eyelid elevation, eye elevation, ADduction, depression in ABduction, efferent (pupil)
IV	Trochlear	Eye intorsion, depression in ADduction
V	Trigeminal	Facial (and corneal) sensation, mastication muscles
VI	Abducens	Eye ABduction
VII	Facial	Facial movement, taste fibres
VIII	Vestibular Cochlear	Balance and hearing
	Cochlear	
IX	Glossopharyngeal	Sensation – soft palate, taste fibres
X	Vagus	Cough, palatal and vocal cord movements
XI	Accessory	Head turning, shoulder shrugging
XII	Hypoglossal	Tongue movement



Optic nerve (Cranial Nerve II**) and visual system**

Visual field defects



Visual fields that accompany damage to the visual pathways

- 1) Optic nerve: **unilateral amaurosis**.
- 2) Lateral optic chiasm: Grossly incongruous, **incomplete** (contralateral) **homonymous hemianopia**.
- 3) Central optic chiasm: **bitemporal hemianopia**.
- 4) Optic tract: Incongruous, **incomplete homonymous hemianopia**.
- 5) Temporal (Meyer's) loop of the optic radiation: congruous partial or complete (contralateral) homonymous **superior quadrantanopia**.
- 6) Parietal (superior) projection of the optic radiation: congruous partial or complete homonymous **inferior quadrantanopia**.
- 7) Complete parieto-occipital interruption of the optic radiation: **Complete** congruous **homonymous hemianopia** with psychophysical shift of the foveal point, often sparing central vision and resulting in "**macular sparing**".
- 8) Incomplete damage to the visual cortex: Congruous homonymous scotomas, usually encroaching at least acutely on central vision.

The main points for the exam are:

- left homonymous hemianopia means **visual field defect to the left**, i.e. **Lesion of right optic tract**
- homonymous quadrantanopias: **PITS** (**P**arietal-**I**nferior, **T**emporal-**S**uperior)
- incongruous defects = **optic tract lesion**; incongruous defect is incomplete or asymmetric
- congruous defects = **optic radiation lesion** or **occipital cortex**
A congruous defect simply means complete or symmetrical visual field loss and conversely an.

Homonymous hemianopia:

- incongruous defects: lesion of optic tract
- congruous defects: lesion of optic radiation or occipital cortex
- macula sparing: lesion of occipital cortex ???

Homonymous quadrantanopias*

- **superior**: lesion of temporal lobe
- **inferior**: lesion of parietal lobe
- mnemonic = **PITS** (Parietal-Inferior, Temporal-Superior)

Bitemporal hemianopia:

- lesion of optic chiasm
- upper quadrant defect > lower quadrant defect = inferior chiasmal compression, commonly a pituitary tumour
- lower quadrant defect > upper quadrant defect = superior chiasmal compression, commonly a craniopharyngioma

*this is very much the 'exam answer'. Actual studies suggest that the majority of quadrantanopias are caused by occipital lobe lesions. Please see the following link for more details:

<http://www.ncbi.nlm.nih.gov/pubmed/9109741>

Amaurosis fugax

- Unilateral transient loss of vision that develops over seconds
- Remains for up to five minutes and resolves over 10-20 minutes.
- The only feature that differentiates the middle cerebral artery syndrome from the carotid artery syndrome is amaurosis fugax.

Leber's optic atrophy:

- usually affects young men
- It causes sequential optic neuropathies in days to weeks.
- It is typically **painless** and severe. Visual acuity fails to improve.
- Mutations in the MT-ND1, MT-ND4, MT-ND4L, and MT-ND6 genes cause Leber hereditary optic atrophy. These genes are contained in mitochondrial DNA.
- A significant percentage of people with a mutation that causes Leber hereditary optic atrophy do not develop any features of the disorder.
- Specifically, more than 50% of males with a mutation and more than 85% of females with a mutation never experience vision loss or related medical problems.

☒ Optic neuritis is usually painful, and visual acuity improves over a matter of weeks.

☒ Giant cell arteritis affects elderly patients.

☒ Alcohol/tobacco optic neuropathies are usually chronic.

Optic neuritis (ON)

جه في الامتحان 2016/4/6

- It clinically presents as acute or subacute ocular pain worse on movements and visual loss.
- The right answers and typical clinical features are described in the scenario.
- It represents inflammation of the optic nerve and predominantly affects females aged 15 to 45 years.
- The most common form, idiopathic optic neuritis, is a primary demyelinating disease occurring in isolation or as part of multiple sclerosis. Investigations including MRI of the brain can help to predict the risk of conversion to MS and can dictate early intervention with disease-modifying treatments (interferon-beta, glatiramer acetate) that reduces the risk of conversion to MS.
- Acute treatment for idiopathic ON includes intravenous corticosteroid treatment followed by oral prednisolone or observation alone.

Other causes optic neuritis:

- Lyme disease
- Neurosyphilis
- Sarcoidosis
- Systemic lupus erythematosus (SLE) and other connective tissue diseases
- History of exposure to toxins (lead, hyperuricaemia) and
- Medications (tamoxifen, ethambutol, tetracycline, quinine, amiodarone and disulfiram)
- Deficiency of vitamin B12 and folate.

Posterior uveitis

- may present as a painful loss of vision, but usually has gradual development, associated with a history of recent systemic infection or autoimmune disease and clinically manifests with a red eye and obscured view of retina,
- Visual loss due to **retinal detachment** is sudden and has a pattern of floaters, curtain or veil over vision. On examination there is relative afferent pupillary defect and visual field defect by confrontation. The characteristic feature is that the visual loss here is painless.

Central retinal artery occlusion

- Characterised by sudden monocular loss of central and peripheral vision. Patients may have had prior amaurosis fugax.
- On examination there is relative afferent pupillary defect. The visual loss here is usually painless and fundus examination may reveal Hollenhorst plaque in the central retinal artery and "cherry red spot" in the macula.

Giant cell arteritis:

- The most common cause of arteritic anterior ischaemic optic neuropathy (A-AION).
- This condition usually affects older people, is associated with constitutional signs of fatigue, anorexia and weight loss, headache, jaw claudication and markedly high erythrocyte sedimentation rate (ESR).
- On examination there is relative afferent pupillary defect and pale optic nerve swelling in the affected eye with characteristically small optic nerve in the fellow eye. There is usually no eye pain.

The differential diagnoses in a patient presenting with headaches and painful diplopia:

- 1) A posterior communicating aneurysm (**PCA**)
- 2) Ophthalmoplegic migraine
- 3) Pituitary adenoma
- 4) Cavernous sinus thrombosis, or
- 5) A medical mononeuritis.

Third nerve (oculomotor) palsy

Features:

- 1) eye is deviated 'down and out'
- 2) ptosis
- 3) pupil may be dilated (sometimes called a 'surgical' third nerve palsy)

Causes:

- 1) diabetes mellitus
- 2) Vasculitis e.g.
 - ☒ Temporal arteritis,
 - ☒ SLE
- 3) false localizing sign* due to uncal herniation through tentorium if raised ICP
- 4) [cavernous sinus thrombosis](#)
- 5) posterior communicating artery aneurysm (pupil dilated)
- 6) **Weber's syndrome** (branches of the posterior cerebral artery that supply the midbrain):
 - ✓ Ipsilateral 3rd nerve palsy with
 - ✓ contralateral hemiplegia
 - ✓ caused by midbrain strokes
- 7) other possible causes:
 - ☒ amyloid,
 - ☒ multiple sclerosis

*this term is usually associated with sixth nerve palsies but it may be used for a variety of neurological presentations

Painful third nerve palsy = posterior communicating artery aneurysm... painful diplopia

- The third (oculomotor) nerve nucleus complex lies in the midbrain.
- Motor neurones project to the:
 - ☒ Ipsilateral medial rectus, Inferior rectus, Inferior oblique muscle, and
 - ☒ Contralateral superior rectus.
- One central nucleus innervates levator palpebrae superioris bilaterally and, therefore, a midbrain infarct that destroys the central nucleus will result in **bilateral ptosis**.
- Damage to the oculomotor nerve during its course results in ipsilateral ptosis.
- At rest, the globe is diverted downwards and laterally.
- The effect on the pupil is variable, depending on the location of the lesion.
- Compression of the nerve, for example by tumour, posterior communicating or posterior cerebral artery aneurysms, results in an acute total (painful) third nerve palsy with a dilated unreactive pupil.
- Pupillary dilatation occurs early when the nerve is compressed since parasympathetic nerve fibres that innervate the iris are carried on the outside of the nerve bundle.
- Pupillary sparing is characteristic of third nerve lesions caused by infarction in patients more than 50 years of age with diabetes or hypertension.

Trigeminal (V nerve) neuralgia

- Trigeminal neuralgia is a pain syndrome characterised by severe unilateral pain.
- The vast majority of cases are idiopathic but compression of the trigeminal roots by tumours or vascular problems may occur

The International Headache Society defines trigeminal neuralgia as:

- ☒ a unilateral disorder characterised by brief electric shock-like pains, abrupt in onset and termination, limited to one or more divisions of the trigeminal nerve
- ☒ the pain is commonly evoked by light touch, including washing, shaving, smoking, talking, and brushing the teeth (trigger factors), and frequently occurs spontaneously
- ☒ small areas in the nasolabial fold or chin may be particularly susceptible to the precipitation of pain (trigger areas)
- ☒ the pains usually remit for variable periods

Management:

- 1) Carbamazepine is first-line.
- 2) Failure to respond to treatment or atypical features (e.g. < 50 years old) should prompt referral to neurology.

Facial (VII) Nerve

Supply - 'face, ear, taste, tear'

- face: muscles of facial expression
- ear: nerve to stapedius
- taste: supplies anterior two-thirds of tongue
- tear: parasympathetic fibres to lacrimal glands, also salivary glands

Causes of bilateral facial nerve palsy:

- 1) sarcoidosis
- 2) Guillain-Barre syndrome
- 3) polio,
- 4) Lyme disease

Causes of unilateral facial nerve palsy - as above plus

Lower motor neuron

- 1) Bell's palsy
- 2) Ramsay-Hunt syndrome (due to herpes zoster)
- 3) acoustic neuroma
- 4) parotid tumors
- 5) HIV
- 6) multiple sclerosis (may also cause an UMN palsy)
- 7) diabetes mellitus

Upper motor neuron

- stroke

LMN vs. UMN:

- upper motor neuron lesion spares upper face i.e. forehead
- lower motor neuron lesion affects all facial muscles

Bell's palsy

- Acute, unilateral, idiopathic, facial nerve paralysis.
- The aetiology is unknown although the role of the herpes simplex virus has been investigated previously.
- The peak incidence is 20-40 years and the condition is more common in pregnant women.

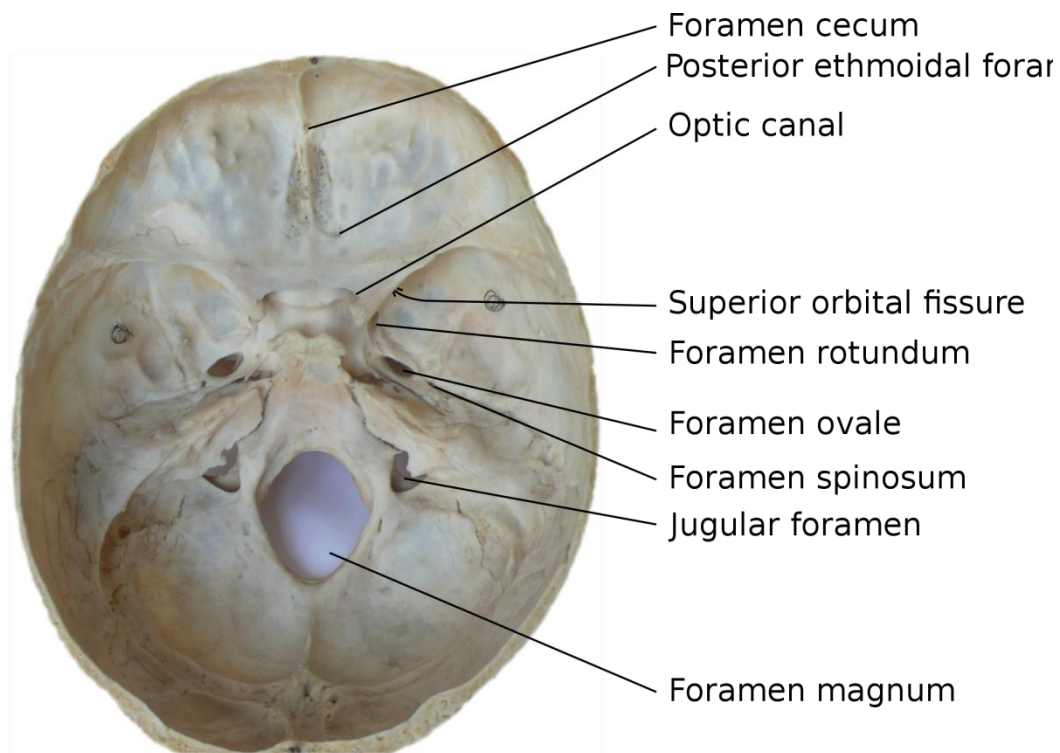
Features:

- 1) lower motor neuron facial nerve palsy - forehead affected
- 2) patients may also notice post-auricular pain (may precede paralysis) مهمة, altered taste, dry eyes, hyperacusis احتداد السمع

Management:

- 1) in the past a variety of treatment options have been proposed including no treatment, prednisolone only and a combination of acyclovir and prednisolone
- 2) Following a National Institute for Health randomized controlled trial it is now recommended that **prednisolone 1mg/kg for 10 days** should be prescribed for patients within 72 hours of onset of Bell's palsy.
- 3) **eye care** is important: prescription of artificial tears and eye lubricants should be considered
- 4) Adding in **acyclovir** gives **no additional benefit**

Prognosis: if untreated around 15% of patients have permanent moderate to severe weakness



Glomus jugulare tumour:

- lesion near the jugular foramen
- presents with a combination of 9th, 10th, 11th and 12th nerve palsies

Foramen magnum syndrome:

- Presents with complex findings usually with a combination of lower cranial nerve dysfunction associated with long tract signs.
- There may be an accompanying occipital headache and neck stiffness and, on occasion, obstruction of the cerebrospinal fluid (CSF) drainage can lead to papilloedema.

Hypoglossal canal syndrome:

- Causes isolated 12th nerve palsy.

- This is a case of **skull base osteomyelitis** and there are clinical clues to it - a diabetic patient with otitis externa signs complicated by unilateral headache and lower motor neurone (LMN) signs, cranial nerve involvement of jugular foramen content and XIIth CN on the affected side with subsequent bulbar palsy presentation and dysphagia.
- This is a rare but potentially life threatening condition affecting people with compromised immunity.
- Typically, *Pseudomonas aeruginosa* is the causative pathogen. Less common pathogens are *Proteus mirabilis*, *Staphylococcus aureus*, *Staphylococcus epidermidis*
- Usually osteomyelitis of the skull is preceded by a local infection, for example:
 - Sinusitis extending to the sphenoid sinuses and involving frontal bone may have serious complications such as cavernous sinus thrombosis
 - Mastoid cell infection and occipital bone osteomyelitis
 - Necrotising otitis externa, complicated by petrous bone osteomyelitis with cranial nerve involvement (most common site of skull base osteomyelitis).
- The clinical scenario depends on the affected part of the skull base in its most common form, that is, petrous bone involvement.
- Patients suffer from chronic otitis externa with otalgia and otorrhoea, which, if untreated, progress and cause unilateral headache, cranial nerve palsies, most commonly IX, X, XI (jugular foramen content) and include also XII nerve form, Villaret's syndrome.
- The usual biochemical picture is raised erythrocyte sedimentation rate (ESR) and normal white cell count (WCC) and C reactive protein (CRP).
- The typical imaging finding are signs of bone destruction especially clivus, shown as hypointensity of bone marrow in the clivus and preclival soft tissue infiltration on MRI T1 weighted images.
- Diagnosis is confirmed by fine needle aspiration (FNA) of tissue and cultures.
- Treatment is with antibiotics

Types of peripheral nerve disease

- **Neuropathy** simply means a pathological process affecting a peripheral nerve or nerves.
- **Mononeuropathy** means a process affecting a single nerve.
- **Mononeuritis multiplex**, several individual nerves are affected.

Polyneuropathy:

- Describes diffuse, symmetrical disease, usually commencing peripherally.
- The course may be acute, chronic, static, progressive, relapsing or towards recovery.
- Polyneuropathies are motor, sensory, sensorimotor and autonomic.
- They are classified broadly into demyelinating and axonal types, depending upon which principal pathological process predominates.
- It is often impossible to separate these clinically.
- Many systemic diseases cause neuropathies.
- Widespread loss of tendon reflexes is typical, with distal weakness and distal sensory loss.

Radiculopathy:

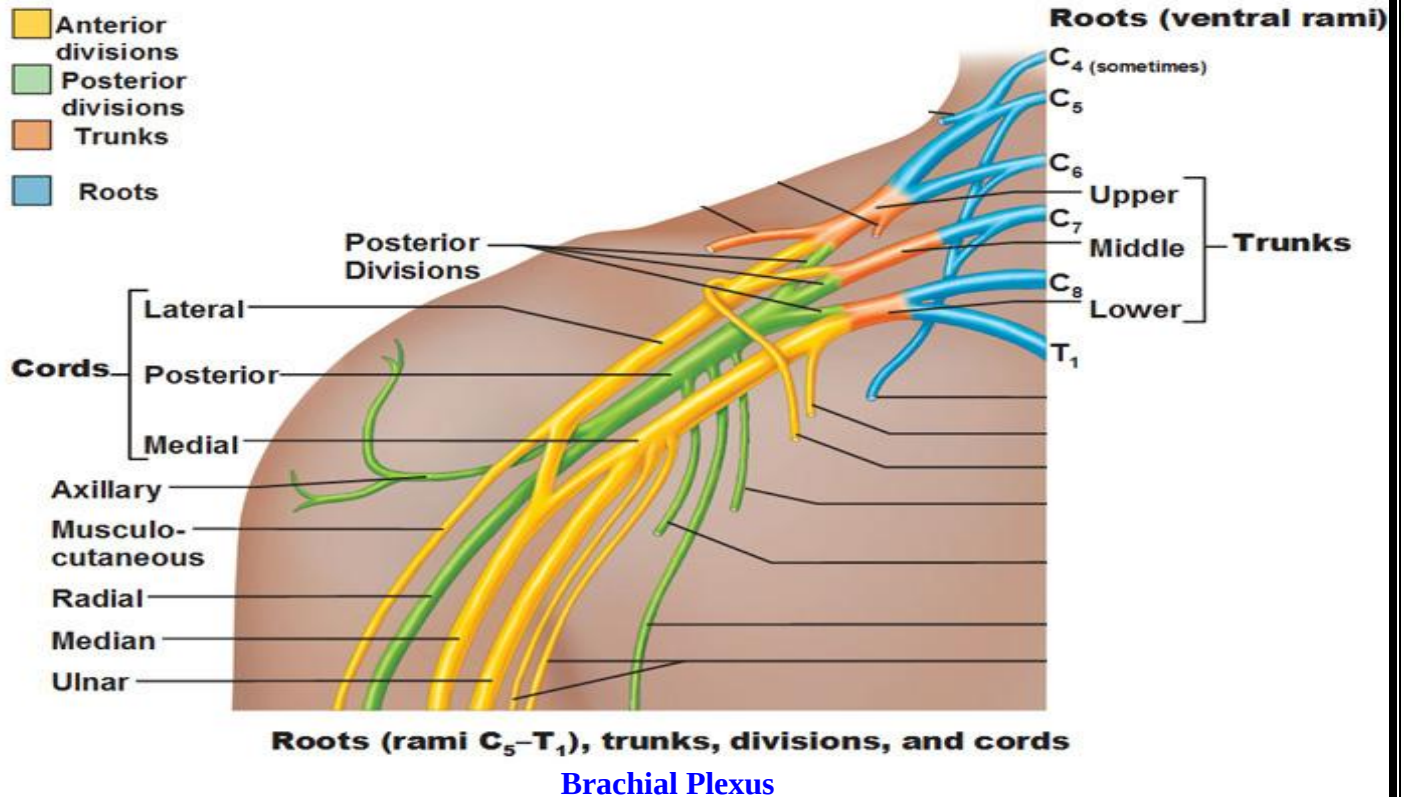
- Means disease affecting nerve roots and plexopathy, the brachial or lumbosacral plexus.
- Diagnosis is made by clinical pattern, nerve conduction/ EMG, nerve biopsy, usually sural or radial, and identification of systemic or genetic disease.

Mononeuropathy

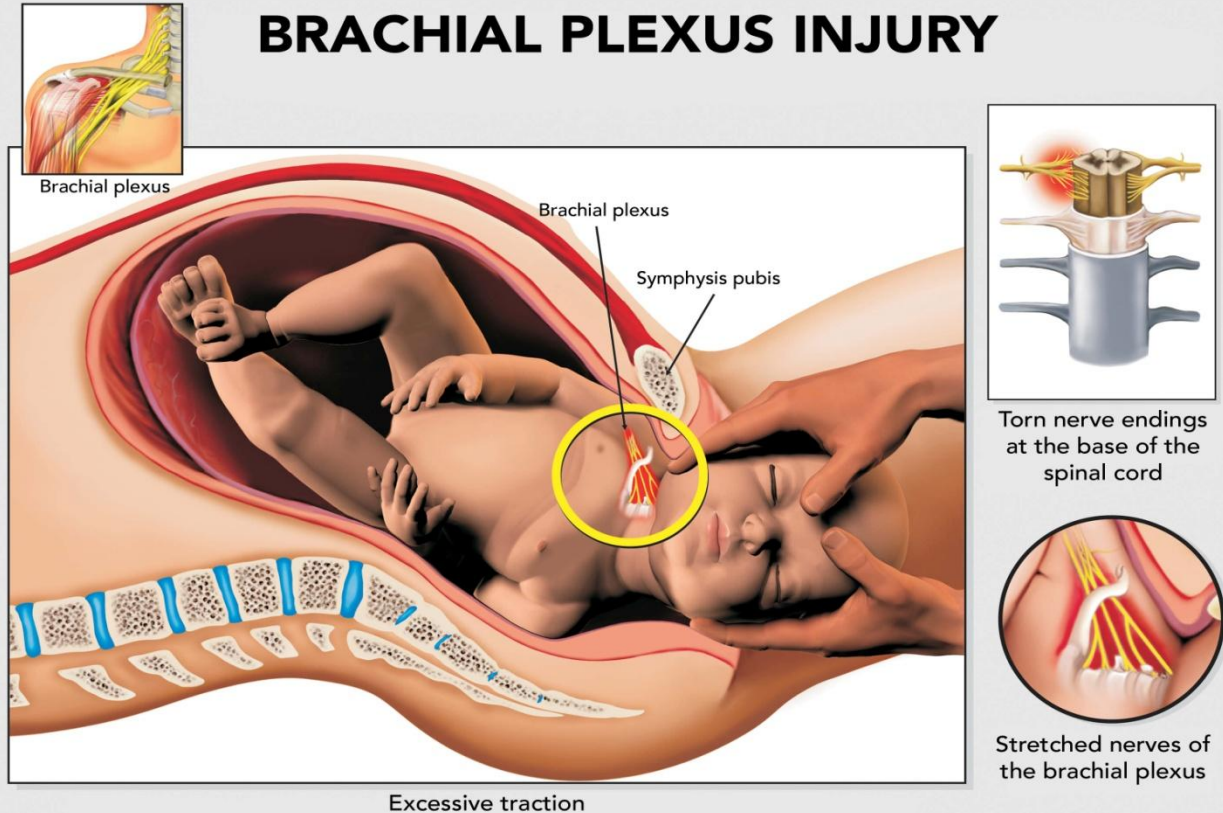
Table 22.24 Nerve compression and entrapment

Nerve	Entrapment/ compression site
Median	Carpal tunnel (wrist)
Ulnar	Cubital tunnel (elbow)
Radial	Spiral groove (of humerus)
Posterior interosseous	Supinator muscle (forearm)
Lateral cutaneous of thigh	Inguinal ligament
Common peroneal	Neck of fibula
Posterior tibial	Tarsal tunnel (flexor retinaculum – foot)

Organization of the Brachial Plexus



BRACHIAL PLEXUS INJURY



Erb's Palsy Pictures - Child Birth Injuries. The most common cause of a brachial plexus birth injury is shoulder dystocia. This occurs when the infant's shoulders can't pass by the mother's pelvic bone, as depicted below

Erb's palsy

- Usually the result of traumatic avulsion of the C5 and C6 roots (commonly occurring during delivery at birth) and causes loss of shoulder abduction and elbow flexion with loss of biceps and brachioradialis reflexes.

Klumpke's palsy:

- often the result of a fall that has been stopped by grasping a fixed object with one hand, involves the C8 and T1 roots and causes weakness of small muscles of the hand and of the long finger flexors and extensors, and a sensory disturbance affecting the medial half of the ring finger and little finger.

A medial cord lesion also affects the C8 and T1 roots.

Neuralgic amyotrophy:

- It usually preceded by an upper respiratory tract infection.
- Pain around the shoulder is the presenting symptom that is usually very severe.
- As the pain starts resolving, weakness begins and usually affects the muscles innervated by the **upper brachial plexus** (C5-6).
- Treatment is conservative. It is usually a self-limiting condition (improvement over weeks to months).
- There have been several cases of elevated cerebrospinal fluid protein with neuralgic amyotrophy.

Neuralgic amyotrophy or a brachial neuritis can be caused by a preceding infection (viral), vaccination, or trauma. It can be total or segmental affecting only specific nerves of the brachial plexus.

It may affect the long thoracic nerve (C5, C6, and C7), causing a total paralysis of the serratus anterior which fixates the lateral scapula to the chest wall. Cause weakness in raising the right arm above the head, with winging of the scapula when the outstretched arm was pushed against resistance

Symptoms and signs of a C6 root lesion include

- Paraesthesias in the thumb or lateral distal forearm
- Weakness of brachioradialis, biceps, or triceps and
- Diminished biceps and brachioradialis reflexes in conjunction with an increased triceps reflex.

Patients do not always present with all of these features but the key finding here is the inverted upper limb reflexes (brisk triceps and diminished biceps and brachioradialis).

Median nerve

- arises from lateral and medial cords of the brachial plexus (C6-8, T1)

Motor to (LOAF):

- Lateral two lumbricals
- Opponens pollicis
- Abductor pollicis brevis
- Flexor pollicis brevis
- ☒ the above three form the thenar eminence muscles
- ☒ Plus also supplies flexor muscles of the forearm
- ☒ The remaining small muscles of the hand are supplied by the ulnar nerve.

Sensory to:

- palmar aspect of lateral (radial) 3 & 1/2 fingers
- Sensation to the thenar eminence is supplied via the **palmar cutaneous branch** of the median nerve, which passes superficially to the flexor retinaculum and is therefore unaffected by carpal tunnel syndrome.

Patterns of damage:

Damage at wrist

- e.g. carpal tunnel syndrome
- paralysis and wasting of thenar eminence muscles
- sensory loss to palmar aspect of lateral (radial) 3 1/2 fingers

Damage at elbow, as above plus:

- unable to pronate forearm
- weak wrist flexion
- ulnar deviation of wrist

Anterior interosseous nerve (branch of median nerve)

- leaves just below the elbow
- results in loss of pronation of forearm and weakness of long flexors of thumb and index

Ulnar nerve

- arises from medial cord of brachial plexus (C8, T1)

Motor to

- medial two lumbricals
- interossei
- adductor pollicis
- hypothenar muscles: abductor digiti minimi, flexor digiti minimi
- flexor carpi ulnaris

Sensory to

- medial 1 & 1/2 fingers (palmar and dorsal aspects)

Patterns of damage

Damage at wrist

- 1) '**claw hand**' - hyperextension of the metacarpophalangeal joints and flexion at the distal and proximal interphalangeal joints of the 4th and 5th digits
- 2) wasting and paralysis of **intrinsic hand muscles** (except lateral two lumbricals)
- 3) wasting and paralysis of **hypothenar muscles**
- 4) **sensory loss** to the medial 1 1/2 fingers (palmar and dorsal aspects)

Damage at elbow

- as above (however, ulnar paradox - clawing is more severe in distal lesions)
- radial deviation of wrist

Radial nerve

- arises from the posterior cord of the brachial plexus (C5-8)

Motor to

- extensor muscles (forearm, wrist, fingers, thumb)

Sensory to

- dorsal aspect of lateral 3 & 1/2 fingers
- however, only small area between the dorsal aspect of the 1st and 2nd metacarpals is unique to the radial nerve

Patterns of damage

In the spiral groove of humerus in midshaft fracture, and also as a result of acute compression, commonly caused by "**Saturday night palsy**", when falls asleep with arm over the side of a chair

- 1) wrist drop
- 2) sensory loss to small area between the dorsal aspect of the 1st and 2nd metacarpals

Axillary damage

- as above +
- paralysis of triceps

Lumbosacral plexopathy:

- **Lesions affecting the entire plexus** will affect all muscle groups causing weakness or paralysis of the leg, areflexia and anaesthesia from the toes, to involve the perianal area.
- **Upper lumbar plexus lesion** will cause weakness of hip flexion and adduction of the thigh and extension of the leg with anaesthesia over the anterior thigh and leg.
- **Lower plexus lesions** will weaken the posterior thigh and foot muscles.

A femoral neuropathy (L2-4)

- Hip weakness, weak knee extension and anaesthesia over the anterior thigh

A common peroneal palsy:

- Cause weakness of dorsiflexion and eversion only and a sensory disturbance affecting the outer lower leg and dorsum of the foot.
- Reflexes would be preserved.

An L5 root lesion:

- Cause weakness of dorsiflexion and inversion and a similar sensory disturbance to a common peroneal neuropathy. Reflexes would be preserved.

The sciatic nerve (L4-S3)

- Supplies both anterior and posterior compartment muscles and also the hamstrings.
- The patient can develop **weakness of the foot, knee flexion and hip extension.**
- Although sciatic nerve palsy is a rarity, it can occur following traumatic fracture of the hip, or as a result of an ill-placed intramuscular injection.
- Other causes include neurofibromas or nerve necrosis secondary to diabetes or infection.

Common peroneal nerve lesion

- The sciatic nerve divides into the tibial and common peroneal nerves.
- Injury often occurs at **the neck of the fibula**
- The most characteristic feature of a common peroneal nerve lesion is **foot drop**
- The commonest cause of **acute foot drop** after prolonged bed rest is entrapment common peroneal neuropathy at the neck of fibula.

Other features include:

- 1) weakness of foot dorsiflexion
- 2) weakness of foot eversion
- 3) weakness of extensor hallucis longus
- 4) wasting of the anterior tibial and peroneal muscles
- 5) sensory loss over the dorsum of the foot and the lower lateral part of the leg

Meralgia paraesthetica

- caused by compression of **lateral cutaneous nerve of thigh**
- typically burning sensation over antero-lateral aspect of thigh

Reflexes

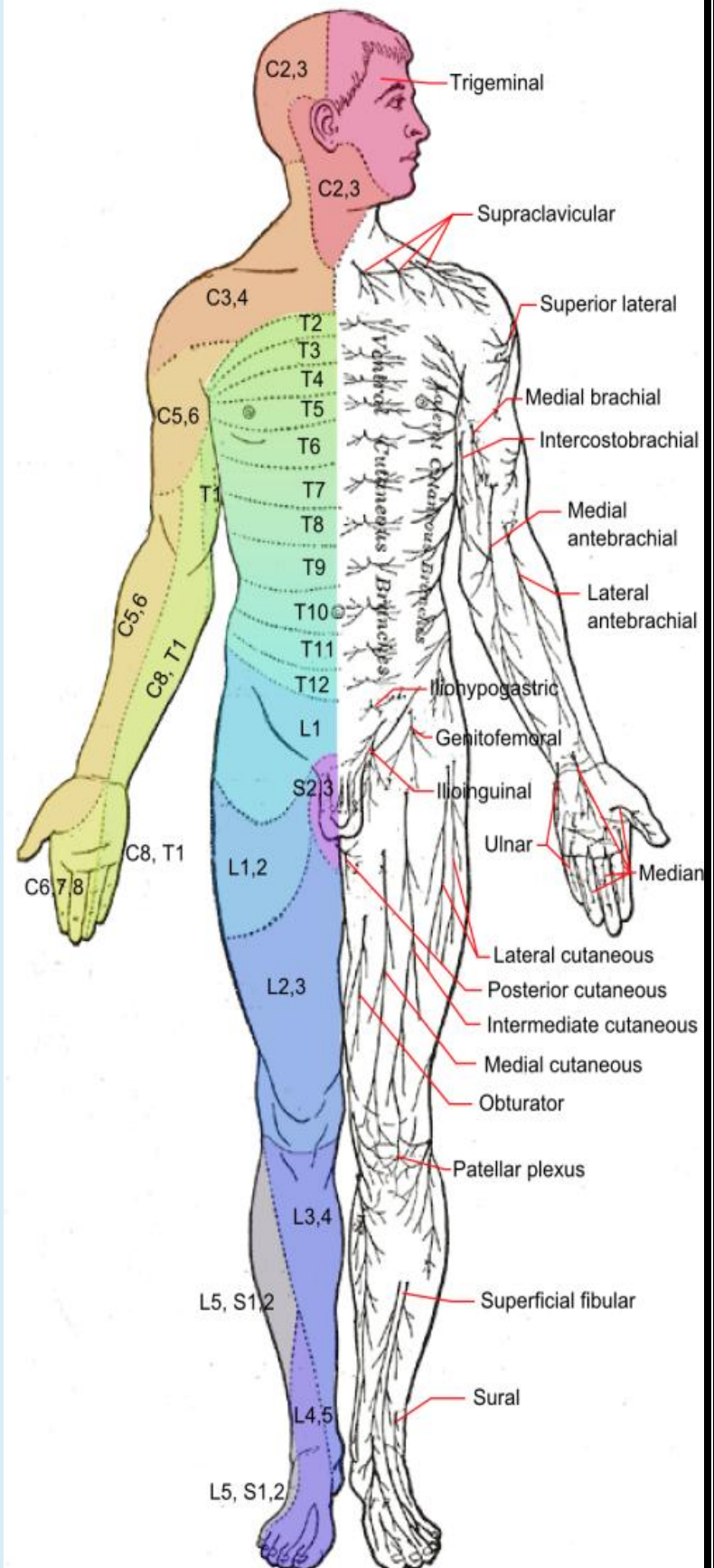
The common reflexes are listed below:

Reflex	Root
Ankle	S1-S2.....1..2
Knee	L3-L4.....3....4
Biceps	C5-C6.....5....6
Triceps	C7-C8.....7....8

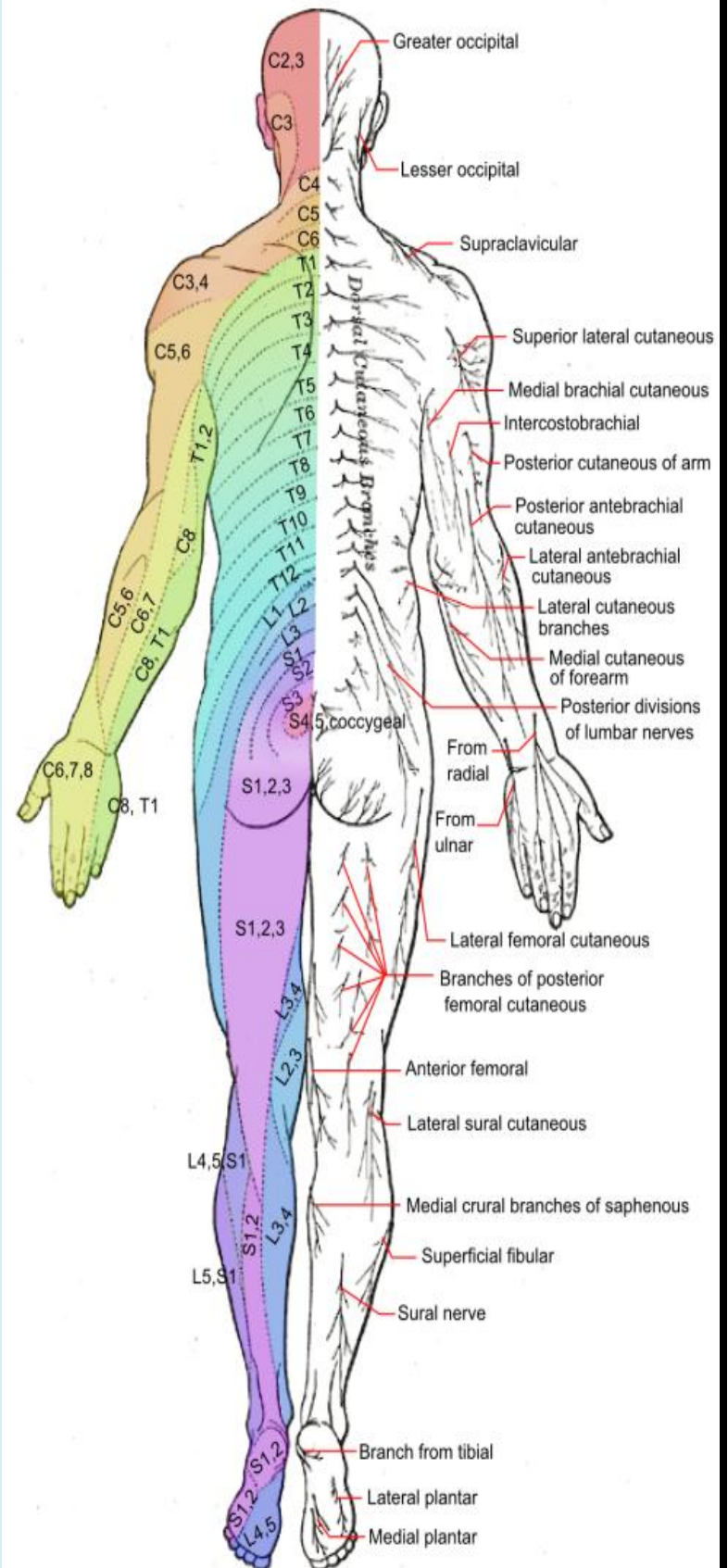
Dermatomes

The table below lists the major dermatome landmarks:

Nerve root	Landmark
C2	Posterior half of the skull (cap)
C3	High turtleneck shirt
C4	Low-collar shirt
C5, C6	Thumb + index finger Make a 6 with your left hand by touching the tip of the thumb & index finger together - C6
C7	Middle finger + palm of hand
C8	Ring + little finger
T4	Nipples T4 at the Teat Pore
T5	Inframammary fold
T7	Xiphoid process
T10	Umbilicus BellybuT-TEN
L1	Inguinal ligament L for ligament, 1 for 1nguinal
L4	Knee caps Down on aLL fours - L4
L5	Big toe, dorsum of foot (except lateral aspect) L5 = Largest of the 5 toes
S1	Lateral foot, small toe S1 = the smallest one
S2, S3	Genitalia



Nerve root	Landmark
C2	Posterior half of the skull (cap)
C3	High turtleneck shirt
C4	Low-collar shirt
C5, C6	Thumb + index finger Make a 6 with your left hand by touching the tip of the thumb & index finger together - C6
C7	Middle finger + palm of hand
C8	Ring + little finger
T4	Nipples T4 at the Teat Pore
T5	Inframammary fold
T7	Xiphoid process
T10	Umbilicus BellybuT-TEN
L1	Inguinal ligament L for ligament, 1 for Inguinal
L4	Knee caps Down on aLL fours - L4
L5	Big toe, dorsum of foot (except lateral aspect) L5 = Largest of the 5 toes
S1	Lateral foot, small toe S1 = the smallest one
S2, S3	Genitalia



Peripheral neuropathy

Motor or sensory loss

Peripheral neuropathy may be divided into conditions which predominately cause a motor or sensory loss

Predominately motor loss:

- 1) Guillain-Barre syndrome
- 2) chronic inflammatory demyelinating polyneuropathy (CIDP)
- 3) diphtheria
- 4) porphyria
- 5) lead poisoning
- 6) hereditary sensorimotor neuropathies (HSMN) - Charcot-Marie-Tooth

Predominately sensory loss

- 1) diabetes
- 2) uremia
- 3) leprosy
- 4) amyloidosis
- 5) alcoholism
- 6) vitamin B12 deficiency

Peripheral neuropathy

Demyelinating vs. Axonal

Demyelinating pathology:

- 1) Guillain-Barre syndrome
- 2) chronic inflammatory demyelinating polyneuropathy (CIDP)
- 3) hereditary sensorimotor neuropathies (HSMN) type I
- 4) paraprotein neuropathy (MGUS, myeloma)
- 5) amiodarone

Axonal pathology:

- 1) alcohol
- 2) diabetes mellitus*
- 3) vitamin B12 deficiency*
- 4) vasculitis
- 5) hereditary sensorimotor neuropathies (HSMN) type II

* may also cause a demyelinating picture

Nerve conduction studies:

Nerve conduction studies (NCS) are useful in determining between axonal and demyelinating pathology

Axonal:

- normal conduction velocity
- reduced amplitude

Demyelinating:

- **reduced conduction velocity**
- normal amplitude

Guillain-Barré syndrome (GBS)

Post-infectious polyradiculopathy

- An immune mediated **demyelination** of **the peripheral nervous system**.
- often triggered by an infection (classically **Campylobacter jejuni**)

Pathogenesis:

- ☒ cross reaction of **antibodies** with **gangliosides** in the peripheral nervous system
- ☒ correlation between **anti-ganglioside antibody** (e.g. **anti-GM1**) and clinical features has been demonstrated
- ☒ **anti-GM1** antibodies in **25%** of patients, (**anti-GD3** also may be found)

Features:

- 1) **The characteristic feature** of GBS is progressive **weakness** of all four limbs.
 - ☒ The weakness is classically ascending i.e. the **lower extremities** are affected **first**;
 - ☒ However it tends to **affect proximal muscles** earlier than the distal ones.
- 2) Sensory symptoms tend to be mild (e.g. distal **paraesthesia**) with **very few sensory signs**. (**Sensory exam. Almost normal**)
- 3) Some patients experience **back pain** in the initial stages of the illness
- 4) **areflexia**
- 5) cranial nerve involvement e.g. **diplopia**
- 6) autonomic involvement: e.g. **urinary retention**
- 7) **Papilloedema**: thought to be secondary to reduced CSF resorption (less common)

Investigations:

- 1) **CSF:**
 - ☒ **High CSF protein** with **normal cell count** are typical features (cytological dissociation)

CSF proteins may be normal at the onset of symptoms in Guillain-Barré syndrome and increase later on.

- 2) Performing **FVC** as a monitor of lung function
- 3) Nerve conduction studies (including F waves for the proximal spinal root, looking for widespread demyelination)

Management:

- 1) **plasma exchange**
 - 2) **IV immunoglobulins** (IVIG): as effective as plasma exchange.
- ☒ No benefit in combining both treatments.
 - ☒ IVIG may be easier to administer and tends to have fewer side-effects
 - ☒ steroids and immunosuppressants **have not been shown to be beneficial**
 - ☒ **FVC** q4hrs regularly to **monitor respiratory function**

Prognosis:

- 20% suffer permanent disability,
- 5% die

Poor prognostic features:

- age > 40 years
- previous history of a diarrhoeal illness (specifically Campylobacter jejuni)
- poor upper extremity muscle strength
- high anti-GM1 antibody titre
- need for ventilatory support
- There is currently contradictory evidence as to whether a gradual or rapid onset of GBS is associated with a poor outcome

Miller Fisher syndrome

- variant of Guillain-Barre syndrome
- Associated with:
 - ✓ ophthalmoplegia,
 - ✓ ataxia
 - ✓ areflexia
- The **eye muscles** are typically **affected first**
- usually presents as a **descending paralysis** rather than ascending as seen in other forms of Guillain-Barre syndrome
- **Anti-GQ1b** antibodies are present in 90% of cases

Chronic inflammatory demyelinating polyneuropathy (CIDP)

A subacute sensory and motor peripheral neuropathy

- progressive weakness and impaired sensory function in the upper and lower limbs
- The cause of the demyelination is not understood, but it is more common in young adults and in men.
- It presents with **abnormal sensation** (which typically begins distally), **weakness** of the limbs, **areflexia** and fatigue.
- Treatment for CIDP includes corticosteroids, plasmapheresis and intravenous immunoglobulin.
- Physiotherapy is an effective adjunct.
- The course varies widely, and patients may be left with residual neurology or suffer a number of relapses.
- CIDP is closely linked to GBS, and is thought by some to be its chronic counterpart.

Acute Disseminated Encephalomyelitis (ADEM):

- An acute demyelinating disorder.
- It is thought to be an autoimmune response to myelin basic protein as a result of a viral illness or vaccination.
- This patient presents with a short history of flu-like illness, with subsequent development of focal neurology, fever and encephalopathy.
- Treatment is usually with intravenous steroids, however in some cases where steroids have failed, intravenous immunoglobulin or plasmaphoresis have been used with good effect.

Metabolic, Toxic and Vitamin Deficiency Neuropathy:

Metabolic

- Diabetes mellitus
- Uraemia
- Hepatic disease
- Thyroid disease
- Porphyria
- Amyloid disease
- Malignancy
- Refsum's disease
- Critical illness

Toxic

- Drugs ([Table 22.26](#))
- Alcohol
- Industrial toxins, e.g. lead, organophosphates

Vitamin deficiency

- B₁ (thiamin)
- B₆ (pyridoxine)
- Nicotinic acid
- B₁₂

Drug-related neuropathies

Hereditary sensorimotor neuropathies, e.g. Charcot–Marie–Tooth

Other polyneuropathies:

- Neuropathy in cancer
- Neuropathies in systemic diseases
- Autonomic neuropathy
- HIV-associated neuropathy
- Critical illness neuropathy

Toxic neuropathies

Alcoholic neuropathy

- secondary to both direct toxic effects and reduced absorption of B vitamins
- sensory symptoms typically present prior to motor symptoms
- affects mainly **spinothalamic** pathway

Neurologic effects of alcohol

- Acute Alcohol intoxication:
 - Disturbance of balance, gait and speech
 - Coma
 - Head injury and sequelae
- Alcohol withdrawal:
 - Morning shakes
 - Tremor
 - Delirium tremens
- Thiamin deficiency:
 - Polyneuropathy
 - Wernicke–Korsakoff
- Epilepsy
- Acute intoxication
- Alcohol withdrawal
- Hypoglycaemia
- Cerebellar degeneration
- Cerebral infarction
- Cerebral atrophy, dementia
- Central pontine myelinolysis
- Marchiafava–Bignami syndrome (corpus callosum)
- degeneration, rare

Drugs causing peripheral neuropathy

- nitrofurantoin, metronidazole
- isoniazid
- amiodarone
- vincristine
- TCAs
- Phenytoin

Vitamin deficiencies

- Vitamin deficiencies cause nervous system damage that is potentially reversible if treated early, and progressive if not.
- Deficiencies, often of multiple vitamins, develop in malnutrition.

Thiamin (vitamin B1)

- Dietary deficiency causes **beriberi**
- Its principal features are **polyneuropathy** and **cardiac failure**.
- Thiamine deficiency also leads to **Wernicke's encephalopathy** and **Korsakoff psychosis**.
- Alcohol is the commonest cause in western countries and, rarely, anorexia nervosa or vomiting of pregnancy

Wernicke's encephalopathy

- A neuropsychiatric disorder caused by **thiamine deficiency** which is most commonly seen in **alcoholics**.
- Rarer causes include: **persistent vomiting**, **cancer stomach**, **dietary deficiency**.
- A classic triad of **acute mental confusion**, **ophthalmoplegia** and **ataxia** may occur.
- In Wernicke's encephalopathy **petechial haemorrhages** occur in a variety of structures in the brain including the **mamillary bodies** and **ventricle walls**

Features:

- 1) **nystagmus** (the most common ocular sign)
- 2) **ophthalmoplegia** Oculomotor dysfunction
- 3) **ataxia**
- 4) **confusion**, altered GCS
- 5) peripheral sensory neuropathy

Investigations:

- decreased red cell **transketolase**
- MRI **petechial haemorrhages** occur in a variety of structures in the brain including the **mamillary bodies** and **ventricle walls**

Treatment:

- urgent replacement of thiamine

NB intravenous glucose prior to giving thiamine can significantly worsen Wernicke's encephalopathy.

Wernicke–Korsakoff syndrome: (from Kumar)

- This thiamin-responsive
- Encephalopathy is due to damage in the brainstem and its connections.
- It consists of:
 - Eye signs:
 - ✓ nystagmus,
 - ✓ bilateral lateral rectus palsies,
 - ✓ conjugate gaze palsies
 - Ataxia:
 - ✓ broad-based gait,
 - ✓ cerebellar signs and
 - ✓ vestibular paralysis
 - Cognitive change:
 - ✓ acutely stupor and coma,
 - ✓ Later a **Korsakoff's amnestic syndrome** with confabulation.
- Wernicke–Korsakoff syndrome is underdiagnosed.
- Thiamine should be given parenterally if the diagnosis is a possibility.
- Untreated Wernicke–Korsakoff syndrome commonly leads to an irreversible amnestic state.
- Erythrocyte transketolase activity is reduced but the test is rarely available.

Vitamin B₂ or riboflavin deficiency can cause angular cheilitis, glossitis and seborrhoeic dermatitis.

Vitamin B₃ or niacin deficiency can cause dermatitis, dementia and diarrhoea (pellagra).

Vitamin B₉ or folic acid deficiency causes a macrocytic anaemia.

Vitamin B₁₂ deficiency causes a macrocytic anaemia, peripheral neuropathy and cognitive impairment.

Pyridoxine (vitamin B₆)

- Deficiency causes a mainly sensory neuropathy.
- In practical terms this is seen as limb numbness developing during anti-TB therapy in slow isoniazid acetylators
- Prophylactic pyridoxine 10 mg daily is given with isoniazid.

Isoniazid toxicity ⇒ intractable seizures and profound metabolic acidosis with high anion gap
Intravenous pyridoxine (vitamin B₆) is the treatment of choice here.

Vitamin B₁₂ deficiency:

- B₁₂ (cobalamin) Deficiency causes damage to the spinal cord, peripheral nerves and brain.
- subacute combined degeneration of spinal cord
- dorsal column usually affected first (joint position, vibration) prior to distal paraesthesia
- sensory ataxia and pseudoathetosis of upper limbs

Subacute combined degeneration of cord

- Combined cord and peripheral nerve damage Due to vitamin B₁₂ deficiency.

Causes:

- 1) Pernicious anaemia is the commonest cause and is usually associated with other autoimmune diseases (for example, hypothyroidism and diabetes).
- 2) Prolonged metformin treatment has also been associated with B12 deficiency (in up to 10% of patients in a large four year clinical trial)
 - ⊗ therefore B12 levels should be screened every few years in patients taking long term metformin

Features:

- ⊗ The combination of absent reflexes and extensor plantar response is typical and is due to co-existing peripheral neuropathy.
- ⊗ Dorsal column involvement with relative sparing of spinothalamic pathways is also typical.
- ⊗ Initially:
 - 1) there is numbness and tingling of fingers and toes,
 - 2) distal sensory loss, particularly posterior column,
 - 3) absent ankle jerks and,
 - 4) with cord involvement, exaggerated knee jerks and extensor plantars
- ⊗ Optic atrophy and retinal hemorrhage may occur.
- ⊗ In later stages:
 - 1) Sphincter disturbance,
 - 2) Severe generalized weakness and dementia develop.

- Macrocytosis with megaloblastic marrow is usual though not invariable in SACD.

Treatment:

- Parenteral B12 reverses nerve damage but has little effect on the cord and brain.
- Without treatment: SACD is fatal within 5 years.

Copper deficiency is a very rare cause of a similar picture

Autonomic neuropathy

Features:

- impotence, inability to sweat
- postural hypotension e.g. drop of 30/15 mmHg
- loss of decrease in heart rate following deep breathing
- pupils: dilates following adrenaline instillation

Causes:

- 1) diabetes,CKD
- 2) Guillain-Barre syndrome
- 3) multisystem atrophy (MSA), Shy-Drager syndrome
- 4) Parkinson's
- 5) infections: HIV, Chagas' disease, neurosyphilis
- 6) drugs: antihypertensives, tricyclics
- 7) craniopharyngioma

Gastroparesis:

Symptoms include:

- 1) erratic blood glucose control,
- 2) bloating and
- 3) vomiting

Management options include: (prokinetic agents)

- 1) metoclopramide,
- 2) domperidone or
- 3) erythromycin

Diabetic neuropathy:

- Diabetic peripheral neuropathy usually goes in parallel with retinopathy and nephropathy.
 - affects mainly the spinothalamic pathway
 - NICE updated it's guidance on the management of neuropathic pain in 2013.
 - Diabetic neuropathy is now managed in the same way as other forms of neuropathic pain:
- 1) **first-line treatment:** amitriptyline, duloxetine, gabapentin or pregabalin
 - 2) if the first-line drug treatment does not work try one of the other 3 drugs
 - 3) tramadol may be used as 'rescue therapy' for exacerbations of neuropathic pain
 - 4) topical capsaicin may be used for localised neuropathic pain (e.g.postherpetic neuralgia)
 - 5) pain clinics may be useful in patients with resistant problems

Neuropathic pain:

- Neuropathic pain may be defined as pain which arises following damage or disruption of the nervous system.
- It is often difficult to treat and responds poorly to standard analgesia.

Examples include:

- 1) diabetic neuropathy
- 2) post-herpetic neuralgia
- 3) trigeminal neuralgia
- 4) prolapsed intervertebral disc

NICE updated their guidance on the management of neuropathic pain in 2013:

- 1) first-line treatment: amitriptyline, duloxetine, gabapentin or pregabalin
- 2) if the first-line drug treatment does not work try one of the other 3 drugs
- 3) tramadol may be used as 'rescue therapy' for exacerbations of neuropathic pain
- 4) topical capsaicin may be used for localised neuropathic pain (e.g. postherpetic neuralgia)
- 5) pain clinics may be useful in patients with resistant problems

Please note that for some specific conditions the guidance may vary. For example **carbamazepine** is used first-line for trigeminal neuralgia

Autonomic dysreflexia: (**bradycardia** & **HTN** IN Quadriplegic pt)

- A poorly understood condition associated with abnormal control of the autonomic nervous system in quadriplegic patients.
- It affects approximately 85% of patients with a lesion above C6
- may be triggered by cystitis, retention of urine or a blocked catheter or constipation
- The increased sympathetic activity results in vasoconstriction and hypertension with stimulation of the carotid and aortic baroreceptors.
- These in turn respond via the vasomotor centre with increased vagal tone resulting in a bradycardia but reduced sympathetic tone with vasodilatation not possible due to the cord damage.
- Treatment relies upon recognition and **removal of the noxious stimulus**.
- **Vasodilators** such as **calcium antagonists** may be used to treat the hypertension.

Genetic neuropathies

Hereditary sensorimotor neuropathy (HSMN)

- Hereditary sensorimotor neuropathy (HSMN) is a relatively new term which encompasses Charcot-Marie-Tooth disease
- also known as peroneal muscular atrophy
- Over 7 types have been characterised - however only 2 are common to clinical practice

☒ **HSMN type I:** primarily due to demyelinating pathology

☒ **HSMN type II:** primarily due to axonal pathology

HSMN type I:

- ☒ **autosomal dominant**
- ☒ due to defect in PMP-22 gene (which codes for myelin)
- ☒ features often start at puberty
- ☒ motor symptoms predominate
- ☒ distal muscle wasting, pes cavus **قدم جوفاء**, clawed toes
- ☒ foot drop, leg weakness often first features

HSMN type I: **كلها فى القدم والرجلين** -distal muscle wasting, pes cavus, clawed toes
-foot drop, leg weakness often first features

Absent ankle jerks, extensor plantars

Typically caused by lesion producing both upper motor neuron (extensor plantars) and lower motor neuron (absent ankle jerk) signs

Causes:

- 1) subacute combined degeneration of the cord
- 2) motor neuron disease
- 3) Friedreich's ataxia
- 4) syringomyelia
- 5) taboparesis (syphilis)
- 6) conus medullaris lesion (*Cauda equina syndrome*)

Cataplexy

- Sudden and transient loss of muscular tone caused by strong emotion (e.g. laughter, being frightened, crying).
- Around two-thirds (70%) of patients with narcolepsy have cataplexy.
- Attacks typically last from a few seconds to a minute with sudden loss of muscle tone. Partial episodes may cause patients to drop objects, sit down or stop walking suddenly or lose sphincter tone.
- Severe episodes may be associated with complete paralysis apart from respiratory muscles. Longer episodes can be associated with hallucinations. Attacks are usually precipitated by excitement or outbursts of emotion.
- The sensation of being unable to move on going to sleep or on waking is common.
- Features range from buckling knees **التواء الركبة** to collapse.
- **Clomipramine**, **fluoxetine** and **sertraline** are used in the management of cataplexy.

Narcolepsy (hypnolepsy)

- A chronic neurological disorder involving the loss of the brain's ability to regulate sleep-wake cycles normally.
- People with narcolepsy experience frequent excessive daytime sleepiness, comparable to how people who don't have narcolepsy feel after 24 to 48 hours of sleep deprivation, as well as disturbed nocturnal sleep which often is confused with insomnia.
- Those with narcolepsy generally experience the REM stage of sleep within 5 minutes of falling asleep, while people who don't have narcolepsy do not experience REM until after a period of slow-wave sleep, which lasts for about the first hour or so of a sleep cycle

In 1999 **modafinil** was approved for the treatment of excessive daytime sleepiness.

There is no cure for narcolepsy.

Amphetamine based compounds such as dexamphetamine have been used to control excessive sleepiness but are used less commonly due to risks of addiction.

MUSCLE DISEASES

Definitions

- Myopathy means a disease of voluntary muscle.
- Myositis indicates inflammation.
- Muscular dystrophies are inherited disorders of muscle cells.
- Myasthenia means fatiguable (worse on exercise) weakness, seen in neuromuscular junction diseases.
- Myotonia is sustained contraction/slow relaxation.
- Channelopathies are ion channel disorders of muscle cells.

Classification

Acquired

- Inflammatory
- Polymyositis
- Dermatomyositis
- Inclusion body myositis
- Viral, bacterial and parasitic infection
- Sarcoidosis

Endocrine and toxic

- Corticosteroids/Cushing's
- Thyroid disease
- Calcium disorders
- Alcohol
- Drugs, e.g. statins

Myasthenic

- Myasthenia gravis
- Lambert–Eaton myasthenic-myopathic syndrome (LEMS)

Genetic dystrophies

- Duchenne
- Facioscapulohumeral
- Limb girdle, and others

Myotonic

- Myotonic dystrophy
- Myotonia congenita

Channelopathies

- Hypokalaemic periodic paralysis
- Hyperkalaemic periodic paralysis

Metabolic

- Myophosphorylase deficiency (McArdle's syndrome)
- Other defects of glycogen and fatty acid metabolism

Mitochondrial disease

Neuromuscular junction disorders

Myasthenia gravis

- An autoimmune disorder resulting in insufficient functioning acetylcholine receptors.
- Antibodies to acetylcholine receptors are seen in 85-90% of cases (Antibodies are less commonly seen in disease limited to the ocular muscles).
- Myasthenia is more common in women (2:1)

Features:

- ☒ The key feature is muscle fatigability
- ☒ Muscles become progressively weaker during periods of activity and slowly improve after periods of rest:
 - 1) extraocular muscle weakness: diplopia
 - 2) ptosis
 - 3) dysphagia
 - 4) proximal muscle weakness: face, neck, limb girdle
 - 5) **never** sensory **symptoms or signs**

Associations:

- 1) thymomas in 15%
- 2) thymic hyperplasia in 50-70%
- 3) autoimmune disorders: **pernicious anaemia, autoimmune thyroid disorder, rheumatoid, SLE**

Investigations:

- 1) **Single fibre electromyography: high sensitivity** (92-100%)
- 2) **Autoantibodies:**
 - ☒ Around **85-90%** of patients have **antibodies to acetylcholine receptors**.
 - ☒ In the remaining patients, **about 40%** are positive for **anti-muscle-specific tyrosine kinase AB**
- 3) **CK normal**
- 4) **CT thorax** to exclude thymoma
- 5) **Tensilon test:** IV edrophonium reduces muscle weakness temporarily
Not commonly used anymore due to the risk of cardiac arrhythmia

Management:

- 1) long-acting anticholinesterase e.g. **pyridostigmine**
- 2) immunosuppression: **prednisolone** initially
- 3) thymectomy

Management of myasthenic crisis:

- 1) **plasmapheresis**
- 2) **intravenous immunoglobulins**

Myasthenia gravis exacerbating factors:

- The most common exacerbating factor is **exertion** resulting in fatigability, which is the hallmark feature of myasthenia gravis.
- Symptoms become more marked during the day

The following drugs may exacerbate myasthenia:

- 1) penicillamine
- 2) quinidine, procainamide
- 3) phenytoin
- 4) beta-blockers
- 5) lithium
- 6) gentamicin, macrolides, tetracyclines quinolones,

Lambert-Eaton syndrome

- Caused by an **antibody** directed against pre-synaptic **voltage gated calcium channel** in the peripheral nervous system
- Seen in association with **small cell lung cancer**, and to a lesser extent **breast** and **ovarian** cancer.
- It may also occur independently as an autoimmune disorder.

Features: **proximal weakness + hyporeflexia + autonomic dysfunction** in a smoker

- 1) **limb girdle weakness:**
 - ☒ affects lower limbs first
 - ☒ repeated muscle contractions lead to **increased muscle strength***
(In contrast to myasthenia gravis)
- 2) **Hyporeflexia**
- 3) **Autonomic symptoms:**
 - ☒ Dry mouth,
 - ☒ impotence,
 - ☒ difficulty micturating
- 4) Ophthalmoplegia and ptosis **not commonly a feature** (unlike in myasthenia gravis)

EMG: incremental response to repetitive electrical stimulation

Management:

- ☒ treatment of underlying cancer
- 1) **immunosuppression**, for example with prednisolone and/or azathioprine
- 2) **3,4-diaminopyridine** is currently being trialled**
- 3) **IVIG** therapy and **plasma exchange** may be beneficial

*in reality this is seen in only 50% of patients and following prolonged muscle use muscle strength will eventually decrease

**works by blocking potassium channel efflux in the nerve terminal so that the action potential duration is increased. Calcium channels can then be open for a longer time and allow greater acetylcholine release to the stimulate muscle at the end plate

Myotonic dystrophy

- Also called dystrophia myotonica.
- Myotonia is sustained contraction/slow relaxation
- Inherited myopathy
- Features develop at around 20-30 years old.
- It affects skeletal, cardiac and smooth muscle.
- There are two main types of myotonic dystrophy, DM1 and DM2.

Genetics:

- **autosomal dominant**
- **a trinucleotide repeat disorder** (Fridrich s ataxia تذكر زي)
- DM1 is caused by a CTG repeat at the end of the DMPK (Dystrophia Myotonica-Protein Kinase) gene on chromosome 19
- DM2 is caused by a repeat expansion of the ZNF9 gene on chromosome 3

DM1	DM2
• DMPK gene on chromosome 19 • Distal weakness more prominent	• ZNF9 gene on chromosome 3 • Proximal weakness more prominent • Severe congenital form not seen

General features:

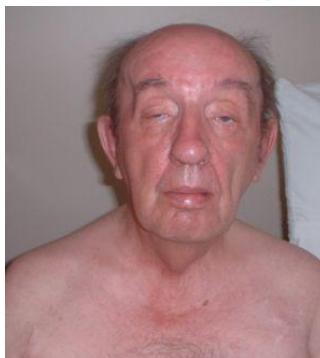
- 1) myotonic facies (long, 'haggard' appearance) 'haggard': صقر قريش
- 2) frontal balding
- 3) bilateral ptosis, cataracts
- 4) dysarthria, dysphagia

Other features:

- 1) myotonia (tonic spasm of muscle)
- 2) weakness of arms and legs (distal initially)
- 3) mild mental impairment
- 4) diabetes mellitus
- 5) testicular atrophy
- 6) cardiac involvement: heart block, cardiomyopathy

Diagnosis can be made on electromyogram (EMG) and **muscle biopsy**.

وشه طويل واصلع عينه بايظه ومبيعرفش يتكلم ومتخلف عقليا
عضلاته ضعيفه ومتقلصه وسكر وقلب وضمور في الخصية
تعرفه لما يسلم عليك..... ما يفكش ايده بسهولة



Focal dystonia

- The patient describes a history suggestive of writers cramp, a focal dystonia characterised by flexion, extension or rotation of the muscles of the hand.
- The underlying pathophysiology is unclear but is thought to relate to a change in plasticity of cortical networks.
- Focal dystonias are distinguished from segmental or generalised dystonias, which involve a greater number of muscle groups.
- Focal dystonias are often relieved by a geste antagoniste, in which palpation of another unaffected part of the body leads to relief of symptoms, thought to be a result of alternative sensory input to cortical networks with altered plasticity. (Sensory trick)

Mitochondrial diseases

- Whilst most DNA is found in the cell nucleus, a small amount of double-stranded DNA is present in the mitochondria.
- It encodes protein components of the respiratory chain and some special types of RNA

Mitochondrial inheritance has the following characteristics:

- 1) inheritance is only via the **maternal line** as the sperm contributes no cytoplasm to the zygote
- 2) all children of affected males will not inherit the disease
- 3) all children of affected females will inherit it
- 4) generally encode rare neurological diseases
- 5) **poor genotype: phenotype correlation**
Within a tissue or cell there can be different mitochondrial populations, this is known as **heteroplasmy**

Histology:

- muscle biopsy classically shows '**red, ragged** fibres' due to increased number of mitochondria

Examples include:

- 1) Leber's optic atrophy
- 2) MELAS syndrome: mitochondrial encephalomyopathy lactic acidosis and stroke-like episodes
- 3) MERRF syndrome: myoclonus epilepsy with ragged-red fibres
- 4) Kearns-Sayre syndrome:
 - ☒ onset in patients < 20 years old,
 - ☒ external ophthalmoplegia, Ptosis
 - ☒ retinitis pigmentosa
 - ☒ Heart block
- 5) sensorineural hearing loss

DVLA

Neurological disorders:

The guidelines below relate to car/motorcycle use unless specifically stated. For obvious reasons, the rules relating to drivers of heavy goods vehicles tend to be much stricter

Specific rules

- stroke or TIA: **1 month** off driving
- multiple TIAs over short period of times: **3 months** off driving
- First seizure: **6 months** off driving*.
- patients with **established epilepsy** they must be fit free **12 months** before being able to drive
- pituitary tumour: **craniotomy**: **6 months**; **trans-sphenoidal** surgery 'can drive when there is no debarring residual impairment likely to affect safe driving'
- **craniotomy** e.g. For meningioma: **1 year** off driving**
- **narcolepsy/cataplexy**: cease driving on diagnosis, can restart once 'satisfactory control of symptoms'
- **chronic neurological disorders** e.g. multiple sclerosis, motor neuron disease: DVLA should be informed, complete PK1 form (application for driving licence holders state of health)

Syncope

- simple faint: **no** restriction
- single episode, explained and treated: **4 weeks** off
- single episode, unexplained: **6 months** off
- two or more episodes: **12 months** off

*previously rule was 12 months. It is now 6 months off driving if the licence holder has undergone assessment by an appropriate specialist and no relevant abnormality has been identified on investigation, for example EEG and brain scan where indicated

**if the tumour is a benign meningioma and there is no seizure history, licence can be reconsidered 6 months after surgery if remains seizure free

Paraneoplastic syndromes affecting nervous system:

Lambert-Eaton myasthenic syndrome:

- associated with SCLC (also breast and ovarian)
- antibody directed against pre-synaptic voltage gated calcium channel in the peripheral nervous system
- can also occur independently as autoimmune disorder

Anti-Hu:

- associated with SCLC and neuroblastomas
- sensory neuropathy - may be painful
- cerebellar syndrome
- encephalomyelitis

Anti-Yo:

- associated with ovarian and breast cancer
- cerebellar syndrome

Anti-GAD antibody:

- associated with breast, colorectal and SCLC
- stiff person's syndrome or diffuse hypertonia

Anti-Ri:

- associated with breast and SCLC
- ocular opsoclonus-myoclonus

Restless legs syndrome (RLS)

- A syndrome of spontaneous, continuous lower limb movements that may be associated with paraesthesia.
- It is extremely common, affecting between 2-10% of the general population.
- Males and females are equally affected and a family history may be present

Clinical features:

- 1) Uncontrollable urge to move legs (akathisia).
- 2) Symptoms initially occur at night but as condition progresses may occur during the day.
- 3) Symptoms are worse at rest
- 4) paraesthesias e.g. 'crawling' الزحف or 'throbbing' sensations
- 5) movements during sleep may be noted by the partner - periodic limb movements of sleeps (PLMS)

Causes and associations:

- 1) there is a positive family history in 50% of patients with idiopathic RLS
- 2) **iron deficiency anaemia**, Mg or folate deficiency
- 3) uraemia
- 4) diabetes mellitus
- 5) pregnancy
- 6) COPD
- 7) Parkinson's

The diagnosis is clinical although bloods to exclude iron deficiency anaemia may be appropriate

Management:

- 1) simple measures: walking, stretching, massaging affected limbs
- 2) treat any iron deficiency
- 3) **dopamine agonists** are **first-line treatment** (e.g. Pramipexole, ropinirole)
- 4) benzodiazepines
- 5) gabapentin

Spastic paraparesis

Spastic paraparesis describes an upper motor neuron pattern of weakness in the lower limbs

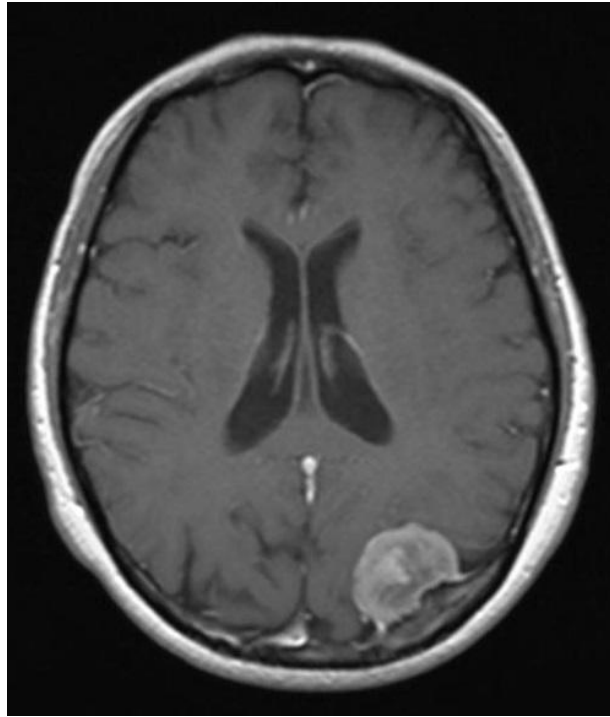
Causes

- 1) demyelination e.g. multiple sclerosis
- 2) parasagittal meningioma
- 3) cord compression: trauma, tumour
- 4) osteoarthritis of the cervical spine
- 5) transverse myelitis e.g. HIV
- 6) syringomyelia
- 7) tropical spastic paraparesis (infection of the spinal cord by Human T-lymphotropic virus HTLV)
- 8) hereditary spastic paraplegia

Brain tumours

The majority **adult tumours are supratentorial**, whereas the majority of **childhood tumours are infratentorial**

Type of tumour	Features
Glioblastoma multiforme	• The most common primary brain tumour in adults. • Histology: Pleomorphic tumour cells border necrotic areas
Meningioma	• The second most common primary brain tumour in adults • Histology: Spindle cells in concentric whorls and calcified psammoma bodies
Schwannoma	• Often seen in the cerebellopontine angle: acoustic neuroma • Bilateral schwannoms are seen in neurofibromatosis II • Histology: Antoni A or B patterns are seen. Verocay bodies (acellular areas surrounded by nuclear palisades)
Pilocytic astrocytoma	• The most common primary brain tumour in children • Histology: Rosenthal fibres (corkscrew eosinophilic bundle)
Medulloblastoma	• More common in children • Found exclusively in the posterior fossa • Metastases through the CSF • Histology: Small, blue cells. Rosette pattern of cells with many mitotic figures
Ependymoma	• Commonly seen in the 4th ventricle • May cause hydrocephalus • Histology: perivascular pseudorosettes
Oligodendroma	• Benign, slow-growing tumour common in the frontal lobes • Histology: Calcifications with 'fried-egg' appearance
Haemangioblastoma	• Vascular tumour of the cerebellum • Associated with von Hippel-Lindau syndrome • Histology: foam cells and high vascularity
Pituitary adenoma	• Most common type is a prolactinoma • May present with bitemporal hemianopia
Craniopharyngioma	• Most common paediatric supratentorial tumour • Histology: Derived from remnants of Rathke pouch
Metastases	• Most common type of brain tumour



Meningioma - MRI showing the typical well-circumscribed appearance. A dural tail can be where the tumour 'connects' to the dura. It is seen in around 65% of meningiomas.



Glioblastoma multiforme - CT showing a peripherally enhancing lesion within the left frontal lobe. Note the contrast to the more homogenous meningioma above.

Paraneoplastic neurological syndromes are uncommon but important because they frequently present before the malignancy, and because they cause severe neurological disability.

Examples of these are:

- Limbic encephalitis
- Cerebellar degeneration
- Opsoclonus-myoclonus
- Sensory neuronopathy
- Lambert-Eaton myasthenic syndrome
- Myasthenia gravis
- Dermatomyositis, and
- Polymyositis

Limbic encephalitis

- **Acute to subacute onset of short term memory deficits**, with **relative preservation of other cognitive functions**, is characteristic of limbic encephalitis
- The memory deficits may be noticed after several weeks of depression, personality change, or irritability.
- **Seizures** can occur and are most often partial complex seizures.
- **Olfactory** and **gustatory hallucinations** are common.
- Some patients also develop signs of **diencephalic-hypothalamic dysfunction**, including drowsiness, hyperthermia, hyperphagia, and, less frequently, pituitary hormonal deficits
- In 60% of cases, limbic encephalitis is a paraneoplastic disorder and indicates the presence of an underlying cancer; the most common underlying malignancy is small cell lung carcinoma (SCLC), followed by testicular cancer, thymoma, and Hodgkin's lymphoma
- In contrast to patients with other paraneoplastic neurologic syndromes, in whom magnetic resonance imaging (MRI) is of limited usefulness in helping to establish the diagnosis, patients with limbic encephalitis may present with early MRI changes suggestive of the disorder
- **Typically, the MRI** shows hyperintense abnormalities in the medial aspect of the temporal lobes
- These MRI abnormalities should be differentiated from those in patients with herpes simplex encephalitis, in whom the MRI usually shows signs of oedema, mass effect, contrast enhancement, and, sometimes, areas of hemorrhage.
- Regardless of the tumour type, the neurologic dysfunction usually precedes the diagnosis of cancer.

Most paraneoplastic syndromes respond poorly to immunomodulatory treatment although occasional improvement is seen when the underlying tumour is treated.

Differential diagnosis of acute/subacute encephalopathy is etiologically wide and includes:

- 1) Neurodegenerative (for example sporadic Creutzfeldt-Jakob disease [CJD])
 - 2) Endocrine (hypothyroidism)
 - 3) Toxicological (lead, arsenic poisoning)
 - 4) Nutritional (vitamin B1 deficiency)
 - 5) Infective (HSV, HIV), and
 - 6) Autoimmune causes.⁷
- Due to the diversity of symptoms of limbic encephalitis is likely underdiagnosed
 - In patients without a known cancer, limbic encephalitis may be mistaken for a viral encephalitis or a rapidly developing dementia secondary to a neurodegenerative disorder
 - Symptoms of limbic encephalitis described above supported by MRI findings, in association with cerebrospinal fluid (CSF) changes characteristic of inflammation are highly suggestive of paraneoplastic limbic encephalitis and should prompt testing for **antineuronal antibodies**
 - Among patients with SCLC, the anti-Hu antibody is present in about 50% of those with predominant or isolated symptoms of limbic encephalitis

Chiari malformation (intermittent obstructive hydrocephalus)

- This presents with sudden pressure headache which builds up over a few seconds before losing consciousness with precipitant as cough
- The MRI imaging shows typical features of a Chiari malformation.
- Chiari Type I malformations (small or misshapen posterior fossa leading to protrusion of the cerebellar tonsils through the foramen magnum) are congenital and Associated with hydrocephalus and syringomyelia.
- Type II Chiari malformations occur in childhood with spina bifida.

Permanent vegetative state (PVS):

- Defined as a state of 'wakefulness without awareness'.
- The patient breathes spontaneously without mechanical support, is
- Haemodynamically stable and has cycles of eye closure and opening that resemble a normal sleeping pattern but the patient is inattentive and unaware of his/her surroundings.
- Patients may have spontaneous movements (moaning, grunting, teeth grinding, roving eye movements) and may also smile, laugh and cry without any apparent reason.
- Although there may be eye movement, the eyes do not track a moving object.
- Patients may respond to painful stimuli and may have myoclonus in response to startling stimuli.
- Primitive reflexes may be present.
- Posture may become decorticate and plantar responses are commonly extensor.
- The condition typically occurs when there is irreversible damage to the cerebral hemispheres but the brain stem remains intact.

Causes include

- 1) Head injury
- 2) Hypoxic injury (cardiac arrest, carbon monoxide poisoning)
- 3) Stroke
- 4) Hypoglycaemia
- 5) Intracranial infection
- 6) End-stage degenerative brain disease (for example, Alzheimer's).

Locked-in syndrome:

- A de-afferented state in which patients are aware of themselves and their environment but are unable to respond due to loss of motor and speech function.

The cause is usually either

- ☒ An upper motor neurone lesion of the descending corticospinal tracts in the brainstem (often the pons) below the level of the oculomotor nerve nuclei,
 - ⇒ for example, infarction, hemorrhage, tumour, demyelination, head injury, central pontine myelinolysis after hyponatraemia)
 - or
 - ☒ Widespread lower motor neurone disease (for example, polyneuropathy such as Guillain-Barre syndrome).
- Clinically, the patient is unable to speak or move but patients may be able to open their eyes and may blink in an effort to communicate.

Akinetic mutism:

- A state of profound apathy in which there is evidence of preserved awareness and visual attention and tracking.
- Patients frequently appear as though they are about to speak but do not ('promise of speech').

Coma:

- Comatose patients are unconscious and unresponsive
- unaware of themselves or their environment and cannot be roused into a state of awareness or respond to their environment
- Cyclical eye opening is absent and respiratory function is usually depressed.

Brain death:

- Involves the irreversible loss of all brainstem function.
- Unlike PVS, brainstem function is lost and mechanical respiratory support is required.
- Brain death is, by definition, irreversible and cardiac arrest usually ensues within hours or days of the onset of brain death.
- The diagnosis should be made by two physicians on at least two separate occasions 12-24 hours apart.
- Clinically, the patient is unconscious.
- Absent brainstem function is demonstrated by pupils dilated (mid- or fully) and unreactive to light. Corneal reflex is absent. 'Doll's eye' oculocephalic and caloric reflexes are absent.
- Cough, suck and gag reflexes are absent.
- Ventilatory reflexes are absent and there is no spontaneous respiration when the patient's ventilator is switched off for sufficient period to ensure that the pCO₂ has risen above the threshold for stimulation of respiration.
- Muscle tone is flaccid and there is no spontaneous movement.
- In order to make the diagnosis, these findings should be consistent.

Brain stem death tests include:

- Pupillary light response - CN II and III
- Corneal reflex, response to supraorbital pressure - CN V and VII
- Vestibulo-ocular reflex - CN III and VIII
- Gag reflex - CN IX
- Cough reflex - CN X
- Absence of respiratory effort.

Fat Embolism Syndrome:

- Fat embolism syndrome is *aclinical* diagnosis secondary to the presence of fat globules in the lung parenchyma and circulation that are typically released following long bone fractures.
- It requires high index of suspicion and usually presents 12-72 hours after initial injury.

There is a classic triad of:

- **Respiratory changes:** Dyspnoea, tachypnoea and hypoxaemia are early findings. These may progress to respiratory failure and ARDS requiring mechanical ventilation.
- **Neurological features:** Cerebral emboli produce neurological signs in up to 86% cases. They often occur after onset of respiratory symptoms, with a wide spectrum ranging from mild confusion and drowsiness to seizures. Usually there is an acute confusional state with or without focal signs. Most neurological deficits are transient and reversible.
- **Petechial rash:** This is the final component of the triad to develop and occurs in 60% of cases. Rash is seen in the conjunctiva, mucous membranes, skin folds of upper body particularly neck and axilla, appearing within the first 36 hours.

Patients may also develop:

- pyrexia
- tachycardia
- ECG changes (ST segment depression and right heart strain)
- fluffy retinal exudates
- coagulopathy, and
- renal changes (oliguria, lipiduria, proteinuria or haematuria)

Botulism

- Occurs either from
 - ⇒ gut colonisation (e.g., ingestion of contaminated home-canned food) or
 - ⇒ an infected wound
- Clostridium botulinum spores are widespread in soil and aquatic sediment.

Typical initial features include:

- 1) Diplopia
 - 2) Ptosis
 - 3) Facial weakness
 - 4) Dysarthria, and
 - 5) Dysphagia.
- Later, respiratory difficulty and limb weakness occur.
 - Neuromuscular blockade causes the clinical features.
 - In botulism, the impaired cholinergic transmission also involves autonomic synapses, causing poorly reactive dilated pupils, dry mouth, paralytic ileus and occasionally bradycardia. **Reflexes are depressed or absent**, sensation is normal and cerebrospinal fluid (CSF) is normal in botulism.
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Differential diagnosis of ring-enhancing lesions includes

- Cerebral metastases
- Toxoplasmosis
- Histoplasmosis
- Some primary brain tumours.

Histoplasmosis and tuberculosis are unlikely given the absence of chest symptoms or signs.

Toxoplasmosis infections are often asymptomatic, but symptomatic cases tend to present with an infectious mononucleosis type picture.



Pyogenic brain abscess

The post-contrast CT scan shows a ring-enhancing lesion in the right frontal area with compression of the right lateral ventricle.



Falx calcification